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LUNG CANCER: EXECUTIVE SUMMARY

The smoking and health controversy remains unresolved, despite claims to the contrary. This is clearly demonstrated by the many still unanswered questions about the relationship between smoking and lung cancer. Without resolution of such gaps, it cannot be maintained that cigarette smoking has been proven to cause lung cancer.

The causal hypothesis regarding smoking and lung cancer is based mainly on population (epidemiological) studies in which smoking has been reported to be statistically associated with lung cancer mortality. Although such studies can provide a great deal of information and can identify many variables, such as smoking, diet, genetic predisposition, and occupational exposures, as risk factors for the development of the disease, statistical information alone can never establish causation. The role of statistics is to indicate areas for further investigation -- not to draw conclusions about scientific causation.

Furthermore, epidemiological studies have inherent limitations; they cannot adequately take into account the possible influence of various factors also associated with lung cancer development, such as the genetic backgrounds, the lifestyle choices (e.g., diet), and the environmental exposures (e.g., occupation) which vary among people, particularly among smokers and non-smokers.

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Scientists have long recognized that these factors may be involved in disease development. Consequently, statistical reports on smoking and lung cancer which did not and frequently could not account for these factors are of limited value in establishing causation. As a scientist who believes smoking is involved with lung cancer has conceded, "It is clear that the riddle of smoking and lung cancer will continue to challenge the ingenuity of epidemiologists."¹

Moreover, despite what is alleged about the statistics on smoking and health, some of the data do not support the claimed causal relationship. For example, if smoking causes lung cancer, why do the vast majority of even "heavy" smokers in the studies not develop lung cancer?² Also, under the causal theory, one should expect higher lung cancer death rates in countries where more cigarettes are smoked. However, this is not always the case as shown by the following examples which take into account the latency period or the number of years claimed to be required between exposure to cigarette smoking and the development of lung cancer. In the United Kingdom, where cigarette consumption was lower in 1930 than in the United States, lung cancer death rates in 1950 were higher. Also, Japan had higher consumption in 1930 than Germany, Spain and France, but much lower lung cancer death rates in 1950 than those three countries.³ There are no data to suggest that this has changed in more recent years.

Although hypotheses and theories appear frequently in the literature, no biological mechanisms have been presented to explain how cancer is caused, either by smoking or by any other factor. Hypotheses and theories are, by their very nature, speculative and unproven. In this regard, two scientists have commented, "Although a large number of factors have been associated with the development of malignant neoplasms [cancers] in humans, the mechanisms involved are still largely unknown."⁴ Without knowledge of how an agent causes disease, one must conclude it is still a suspect, not an established cause.

The results of laboratory studies and animal experiments also have been inconclusive. Although thousands of laboratory animals have been exposed to whole fresh tobacco smoke, no animal inhalation experiment with fresh whole tobacco smoke has resulted in the production of human-type lung cancer.⁵ Those who claim that cigarette smoking causes lung cancer have been unable to give a satisfactory explanation for this scientific gap in their chain of evidence.

In conclusion, the deficiencies and weaknesses in the data from the statistical studies and the laboratory investigations and animal experiments point out sharply how much more needs to be learned before the smoking and health controversy can be finally

resolved. Thus, despite the claims that are frequently made about smoking and health, it has not been scientifically established that smoking causes lung cancer.

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REFERENCES

1. Hill, G., "Smoking and Lung Cancer," Archives of Internal Medicine 148: 2538-2539, December 19, 1988.
2. Herrold, K., "Survey of Histologic Types of Primary Lung Cancer in U.S. Veterans," Pathology Annual 7: 45-79, 1972.

Miller, A., "Epidemiology: Problems in the Study of Cancers of Low Incidence and the Need for Collaboration," Journal of the National Cancer Institute 54(2): 299-301, 1975.

Hehlmann, R., "Psychosomatik und Krebs (Psychosomatics and Cancer)," Münchener medizinische Wochenschrift 124(38): 829-830, September 24, 1982. Translation.

3. U.S. Public Health Service, Office on Smoking and Health, The Health Consequences of Smoking: Cancer. A Report of the Surgeon General: 1982, Department of Health and Human Services, Washington, D.C., U.S. Government Printing Office, DHHS Publication No. (PHS) 82-50179, p. 44, 1982.

Burch, P., "The Surgeon General's 'Epidemiologic Criteria for Causality.' A Critique," Journal of Chronic Diseases 36(12): 821-836, 1983.

4. Albanes, D. and M. Winick, "Are Cell Number and Cell Proliferation Risk Factors for Cancer?", Journal of the National Cancer Institute 80(10): 772-775 (at 772), July 20, 1988.
5. U.S. Public Health Service, Office on Smoking and Health, "Mechanisms of Carcinogenesis," The Health Consequences of Smoking: Cancer. A Report of the Surgeon General: 1982, Department of Health and Human Services, Washington, D.C., U.S. Government Printing Office, DHHS Publication No. (PHS) 82-50179, Part III, 171-235, 1982.

Hockett, R.C., Statement, Re: "Smoking Prevention Education Act." In: Hearings Before the Committee on Energy and Commerce, Subcommittee on Health and the Environment, United States House of Representatives, Ninety-Eighth Congress, First Session, 841-851, March 9, 17, 1983.

LUNG CANCER

Foremost among the charges against cigarette smoking is the claim that smoking causes lung cancer. Certainly, there are few, if any, who have not heard that claim. What has not been so well-publicized are the scientific data that are inconsistent with this claim and the vital questions that remain unanswered about the nature of the reported relationship between smoking and lung cancer.

Individuals making this assertion against smoking rely primarily on data from population (epidemiological) studies which have reported a statistical association between smoking and lung cancer. To say that there is a statistical association between a factor such as cigarette smoking and a disease such as lung cancer means that the factor, commonly referred to as a "risk factor," and the disease frequently occur together, or change together. However, it does not mean that a cause-and-effect relationship has been established. Thus, while epidemiological studies can identify risk factors such as smoking, diet, genetic predisposition, and occupational exposures, they cannot answer the important question of whether such associations have causal significance. Moreover, as many scientists have pointed out, demonstration of a biological mechanism and evidence from laboratory studies and animal experiments are needed to bridge the gap between reports of a statistical association and assertions of a causal relationship.

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Without resolution of such gaps, it cannot be maintained that cigarette smoking has been proven to cause lung cancer.

Epidemiological Studies

The causal hypothesis regarding smoking and lung cancer is based mainly on epidemiological studies in which smoking has been reported to be statistically associated with lung cancer mortality. Epidemiological studies are primarily counting studies. Study subjects are divided into groups such as smokers and nonsmokers, deaths from certain specific diseases are counted, death rates are calculated, and comparisons of those death rates are made. It is apparent from this description that epidemiological studies do not in themselves address the biological mechanism for the disease studied.

There are two major types of epidemiological studies generally referred to in this context: retrospective and prospective. A retrospective study selects a group of people with lung cancer, usually hospital patients or hospital deaths, and then tries to go back in time through the use of questionnaires or records or interviews with relatives to collect information on their personal backgrounds, including their smoking histories. In one type of retrospective study, called a case-control study, the persons identified with the disease are compared to a group without the disease called controls. A prospective study identifies a group

of people without lung cancer, and, like a retrospective study, collects information on their personal backgrounds, including their smoking habits, but, unlike a retrospective study, follows them forward in time to observe any disease patterns they may develop. In both types of studies, the data collected are then arranged into various categories and statistical tests applied to determine if one group (smokers) differs from another (nonsmokers) with respect to a particular disease (lung cancer), and if that difference is related to any of the conditions, behaviors or other factors in the lives of the people in the study.

These statistical studies can provide a great deal of information, and perhaps that is why people have become accustomed to saying that statistics "prove" something. However, such epidemiological data alone cannot prove causation. Even the 1964 U.S. Surgeon General's Report on Smoking and Health (frequently referred to as the Terry Report) conceded:

Statistical methods cannot establish proof of a causal relationship in an association. The causal significance of an association is a matter of judgment which goes beyond any statement of statistical probability.¹

Statisticians have attempted to resolve this dilemma in a variety of ways. For example, in 1959, Sir Austin Bradford Hill, who is regarded as a pioneer in the field of medical statistics,

proposed nine criteria which he suggested should be considered before deciding whether a statistical association might be causal. However, after a lengthy discussion of these criteria, he conceded that "None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a sine qua non."²

The authors of the 1964 Surgeon General's Report set out their own criteria for determining whether the reported association between smoking and certain diseases might be causal. These criteria have been utilized in the subsequent reports from the Surgeon General's office, including the 1982 report which focused exclusively on cancer. However, the application of the criteria to the epidemiologic data on smoking and lung cancer has also raised questions. For example, following the publication of the 1982 report, the late Philip R.J. Burch, an eminent medical physicist from the United Kingdom's University of Leeds, contended that an analysis of the epidemiologic data "show that not one of the criteria, plausibly interpreted, is satisfied by the epidemiologic evidence for lung cancer."³ He specifically noted that even though the relative risk ratios for lung cancer mortality for 35 retrospective studies published during the period 1939-1970 and listed in the 1982 report tend to be greater for smokers than nonsmokers, they cover a very wide range, from 1.2 to 36.0 for men and from 0.2 to 5.3 for women. He also noted that similar data

were reported for the eight prospective studies listed in the report. For those studies, the mortality ratios (cigarette smokers vs. nonsmokers) ranged from 3.76 to 14.2 in males and from 2.03 to 5.0 in females. Professor Burch stated, "With ratios showing a range, overall, of more than two orders of magnitude it is not self-evident that any acceptable criterion of consistency has been satisfied."⁴

Professor Burch also pointed out anomalies in the "dose-response" relationship reported in several of the prospective studies. When he analyzed the relative risk of lung cancer -- for onset in British male doctors and death in Japanese males -- as a function of the daily amount of cigarettes smoked, he noted that the calculated risk between the two groups for the same amount smoked differed tremendously:

At first sight, the sheer magnitude of the differences is the most astonishing feature, the relative risk at 38 cigarettes a day being just over 50 for the British doctors and around 5 in Japanese males. A factor of 10 is not readily explained away in 'causal' terms and (small) adjustments for the duration of smoking, etc.⁵

Based on such observations, it is apparent that statistics can only indicate the likelihood that any observed disease patterns are not caused by chance and point to areas for further investigation. As a distinguished American medical statistician once noted:

The cause of cancer is fundamentally not a statistical question, but a biologic one. Statistics, if critically and carefully used, can provide useful 'leads,' but the definitive investigations must come from the biologic sciences, pathology, pharmacology, chemistry and so forth. All of them together must be brought to bear on the problem, if we are to answer the specific question at hand, and the many other questions that are involved.⁶

Moreover, epidemiological studies have inherent limitations. For example, smokers are a self-selected group, which means that they differ from nonsmokers in many ways besides their smoking habits. These include differences in lifestyle, characteristics and behaviors, such as eating habits and exercise patterns. Therefore, comparisons of smokers and nonsmokers made without regard for other differences are subject to scientific criticism. Nor can epidemiological studies adequately take into account the possible influence of such factors as occupational exposures, inherited tendencies to develop certain diseases, and many other biological and behavioral unknowns. Scientists have long recognized that these factors may also be involved in disease development. Consequently, statistical reports on smoking which do not and frequently cannot account for these factors are of limited value in establishing causation. A scientist who personally believes smoking is involved with lung cancer has conceded "it is clear that the riddle of smoking and lung cancer will continue to challenge the ingenuity of epidemiologists."⁷

Inconsistencies in the Epidemiological Studies

Many inconsistencies which raise questions about a causal relationship between smoking and lung cancer have been noted in the epidemiological studies. While the precise meaning of these inconsistencies may be unclear, they show that the case against smoking is not as simple as many people would like to believe.

For example, reports that lung cancer was starting to increase began to appear in the scientific literature before the marked increase in the popularity of cigarette smoking.⁸ A medical doctor who studied these issues noted that English and French physicians were describing the clinical and pathological manifestations of lung cancer in medical journals more than 150 years ago, and that during the latter half of the 19th century, a great number of cases were reported in England, France, Germany and the United States. As he observed, "All this took place a long, long time before cigarette smoking became popular."⁹

There are other inconsistencies. For example, if smoking causes lung cancer, it would be reasonable to expect higher lung cancer rates in countries where more cigarettes are smoked. But that is not always the case, as shown by the following examples which take into account the latency period or the number of years

claimed to be required before cigarette smoking leads to the development of lung cancer, generally about 20 to 30 years. In Great Britain, for example, where cigarette consumption was lower in 1930 than in the United States, lung cancer death rates in 1950 were much higher than in the U.S. On the other hand, in Japan, where cigarette consumption was higher in 1950 than in Germany, Spain and France, lung cancer death rates in 1970 were much lower than in those three countries.¹⁰ There are no data to suggest that this has changed in more recent years.

Also, if smoking causes lung cancer, why do the vast majority of even "heavy" smokers in the epidemiological studies not develop lung cancer?¹¹ Moreover, the same type of epidemiological information used to suggest that lung cancer has increased in smokers suggests that it may also have increased in nonsmokers.¹²

Furthermore, if smoking causes lung cancer, one would expect that the earlier a person starts to smoke and the more he smokes, the sooner he would get lung cancer. Yet nonsmokers and smokers (whether they smoke a little or a lot) all appear to develop the disease at about the same average age.¹³ According to one expert: "That both the age of starting to smoke, and the rate of smoking, should have no appreciable influence on the average age

of onset of lung cancer greatly taxes, if it does not destroy, any causal hypothesis."¹⁴

In addition, if smoking causes lung cancer, it would seem unlikely that there would be large differences in lung cancer rates among different races or ethnic groups and between men and women, regardless of their smoking habits. However, it has been reported that there were fewer cases of lung cancer among Chinese and Japanese women living in Hawaii who smoked than among Hawaiian women who smoked.¹⁵ It has also been reported that women in Hong Kong have a very high rate of lung cancer compared to women in other countries but that they smoke less.¹⁶ In contrast, women in most other countries have lower rates of lung cancer than men, even if they smoke the same amount.¹⁷

Moreover, if smoking caused lung cancer, smokers who inhale cigarette smoke would presumably have higher rates of lung cancer than those who do not inhale. However, in some studies, lower lung cancer rates have been reported among inhalers than among noninhalers.¹⁸

There are other reported observations of a similar nature which appear inconsistent with the causal hypothesis. For example, although inhaled cigarette smoke is distributed equally between both lungs, lung cancers very rarely occur simultaneously in both lungs.

Similarly, cancer rarely occurs in the trachea (the "windpipe"), even though this organ is exposed to more tobacco smoke than either lung, because all the smoke going to the lungs passes through it. Likewise, there has been little change in the incidence of laryngeal cancer over the past decades, even though tobacco smoke also must pass through the larynx (the "voicebox") on its way to the lungs.¹⁹

Such inconsistencies in the epidemiological studies raise serious questions about the causal hypothesis.

Increased Mortality - Real or Apparent?

In recent years, there have been reports of a so-called "epidemic" increase in lung cancer deaths. Some point to this "epidemic" and simultaneous increases in the number of people who smoke as "proof" that smoking causes lung cancer. They find this simplistic explanation appealing, but is it supported by the data? A review of the scientific literature suggests that numerous concerns have been expressed about the reliability of such data. At the very least, such concerns should prompt further serious consideration before attempts are made to answer this question.

Diagnostic Problems

Many scientists have noted that the apparent increase in lung cancer may well reflect a greater ability to detect lung cancer rather than actual increases in the disease itself. They speculate that many lung cancer cases were never discovered in the years before more sophisticated diagnostic techniques were available; that is, lung cancer was underdiagnosed over a long period of time. Many of these same scientists believe that this improved diagnostic capability has been accompanied by another type of diagnostic error, the tendency toward overdiagnosis. In other words, primary lung cancer may now be diagnosed in patients who do not have the disease.

These scientists also believe they know how the tendency toward underdiagnosis may have occurred. Before the middle of this century, doctors were limited in their ability to detect lung cancer because they lacked the principal diagnostic methods -- x-ray, bronchoscopy, and sputum cytology -- now being used. One researcher, who studied the impact of these developments, has observed:

The prodigious increase in lung cancer during the past three decades is not due to the exposure of the population to an alleged carcinogen but is the natural consequence of the widespread use of techniques not previously available.²⁰

Radically improved techniques in more recent years, such as fiberoptic bronchoscopy, mediastinoscopy, computed tomography (CT), and magnetic resonance imaging (MRI), may also have contributed to reported increases in lung cancer.²¹

Support for the hypothesis that the "epidemic" may in part reflect dramatic medical progress can also be found in an examination of non-cancerous lung disease trends. For example, in 1900, the combined crude death rate for respiratory diseases in the United States exceeded 450 per 100,000, but there were no death rates recorded for lung cancer.²² It has been estimated that if only a very small percentage of the cases diagnosed as tuberculosis or other infectious respiratory diseases were actually lung cancer, there would have been relatively little increase in the prevalence of this disease during the first half of this century. More specifically, one researcher has speculated that if only five percent of the deaths attributed to tuberculosis and other respiratory diseases among males over 35 years of age during that period had been lung cancer, it "would have resulted in a twofold lung cancer mortality increase between 1914 and 1950, instead of the recorded 26-fold increase." Likewise, he speculated that if only three per cent of the cases certified as dying of respiratory diseases had actually died of lung cancer, "the increase would have tripled." As he pointed out, "Experienced clinicians will find

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little difficulty in postulating an error of 10 or 20 per cent in the clinical diagnosis of bronchogenic carcinoma, particularly, in an era devoid of x-ray examination, bronchoscopy, thoracotomy, and cytology."²³ Interestingly, recent studies have shown that lung cancer is still being confused with diseases such as tuberculosis, pneumonia and bronchitis.²⁴

The theory that lung cancer has been overdiagnosed in recent years is supported by the results of studies comparing clinicians' diagnoses of lung cancer with autopsy findings of actual causes of death. Such studies have consistently reported large discrepancies. One chest specialist, using microscopic techniques, could confirm only 44 percent of the cases diagnosed by the clinicians as lung cancer.²⁵ He observed that a large part of the difficulty appeared to revolve around the clinician's opinion about the cancer's site of origin. Apparently, the overdiagnosis often occurs because the clinician classifies a lung cancer as primary, or originating in the lung, when in fact the cancer originated elsewhere and then metastasized or spread to the lung to cause a secondary, or metastatic, cancer. Without more detailed study, it is often impossible for the clinician to know that this occurred.

Yet another diagnostic phenomenon called "detection bias" may also be distorting the epidemiological picture regarding smoking and lung cancer. Detection bias occurs when a disease is diagnos-

tically sought more vigorously in people who are exposed to the suspected cause than in people without such exposure. That is, smokers are more likely to be given more diagnostic tests for lung cancer and, therefore, to be diagnosed with the disease than nonsmokers. A medical university research group confirmed its suspicion that such a bias may occur when it analyzed materials from populations of living and deceased patients and determined that lung cancers are less likely to be detected in certain groups of individuals, including nonsmokers.²⁶ The group asserted that its findings "indicate the scientific desirability of a reevaluation" of the reported association between cigarette smoking and lung cancer, "using newer epidemiologic methods that can compensate for the impact of detection bias in observational research."²⁷

In summary, as a U.K. medical physicist has stated, diagnostic error may be largely responsible for the reported increases in lung cancer:

Post-mortem studies of the frequency of lung cancer show that the most important factor in the increase of recorded lung cancer has been clinical diagnostic error. Severe underdiagnosis during the earlier part of the century was eventually followed, in the past decade or so, by overdiagnosis.²⁸

Death Certificates

Another problem involved in assessing reports of an "epidemic" increase in lung cancer and its relationship to cigarette smoking is the type of data researchers rely on to describe large-scale mortality patterns. Most of the data are taken from death certificates. However, studies conducted to determine whether death certificates accurately reflect the actual cause of death have determined that such data may contain many errors. In fact, one researcher asserts that this information is "notoriously inaccurate."²⁹

Errors in death certificate information have been chiefly attributed either to misdiagnosis or to recording errors. Errors related to misdiagnosis occur if the physician incorrectly diagnosed the patient's final disease and that inaccurate information is then entered on the death certificate. This occurs because the physician's diagnosis, usually found in the clinical or hospital record, generally serves as a basis for the cause of death listed on the death certificate unless it is corrected on the basis of laboratory or autopsy results.

Studies utilizing autopsy findings to evaluate the accuracy of clinical diagnoses have reported finding a high rate of error. In those studies, scientists have compared the results

of autopsies, which are considered the best and most reliable source of information on cause of death, with the causes of death listed on the death certificates. Such studies have consistently reported serious error rates between major clinical and autopsy diagnoses, ranging from 20 to 40 percent. Some have even reported error rates up to 60 percent.³⁰

Of the various cancer sites analyzed in such studies, the lung frequently has received special attention from investigators interested in questions of diagnostic accuracy. Their research findings, while differing in some respects, have been consistent on one point: the rate of misdiagnosis of lung cancer has been high. Yet there seemed to be no consistent patterns or obvious explanations for the discrepancies.

Studies have reported that lung cancer has either been overdiagnosed (cases diagnosed as lung cancer turned out to be something else) or underdiagnosed (cases diagnosed as something else turned out to be lung cancer). In one study of 493 cancer cases in a New York City hospital, for example, more than 50 percent of the clinical diagnoses of lung cancer were reportedly found to be incorrect at autopsy.³¹ Conversely, a Boston hospital study reportedly found that a large number of lung cancer cases had been missed clinically. Of the lung cancers confirmed at autopsy, 27 percent had not been diagnosed in the hospital.³² Other studies

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from countries as diverse as Israel,³³ Finland,³⁴ Scotland,³⁵ and the United States³⁶ have also reported varying rates of overdiagnosis and underdiagnosis of lung cancer.

The second major source of errors in death certificate information occurs if the physician makes the correct clinical diagnosis, but it is not properly recorded on the death certificate. In 1979, for example, U.S. researchers compared the hospital diagnosis for nearly 10,000 deaths with the underlying cause of death recorded on the death certificate. They reported finding differences in nearly 30 percent of the cases.³⁷

Various theories have been advanced for such recording errors. It has been suggested, for example, that many physicians may not regard accuracy in death certificate information as an important concern. One pathologist commented that many physicians regard the death certificate as "a document which simply declares that the death was due to natural causes and [which] does not have medico-legal significance." He also noted that "doctors certifying deaths often fail to realise that the information they record is utilised by the statistician for compiling data of epidemiological significance."³⁸ Although physicians may not regard accuracy in recording death certificate information as important, epidemiologists certainly do. As one study noted, such errors

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could cause "interference with accurate epidemiologic association between exposures or risks and various disease outcomes."³⁹

Thus, it is apparent that although mortality statistics are often relied on by investigators, there may be little recognition that such data may contain inaccuracies. Accordingly, extreme caution is warranted in the evaluation of epidemiological studies using mortality data.

Comparisons in Lung Cancer Mortality Trends

One of the methods that have used to support the claim that "epidemic" increases in lung cancer are due to cigarette smoking has been to compare national and international trends in lung cancer mortality with cigarette consumption data. Again, however, such comparisons may be oversimplifications of the data and, therefore, not be reliable. They do not take into account, for example, that as the world's population has grown in size, life expectancy has generally increased markedly. This is significant because many diseases associated with smoking, including lung cancer, are also frequently diseases of old age.⁴⁰ Nor do they take into account the possible influence of changes over time in diagnostic and classification criteria for lung cancer and in coding rules for death certificates that make such trends suspect.

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In general, the information on the cause of death recorded on death certificates in most countries is based on terminology from a coding system called the International Classification of Diseases (ICD). This system has been in effect for many years and, like many such classification systems, it has been and continues to be revised and changed. One of the most recent changes occurred in 1968 and had the very troubling effect of changing the lung cancer disease categories. Prior to that year, lung cancer had been separated into two categories -- lung cancer specified as primary and lung cancer unspecified as either primary or secondary, i.e., metastatic. In that year, however, these two categories were combined into a single classification.⁴¹ Consequently, information obtained from death certificates before 1968 is not generally regarded to be comparable to the information obtained after 1968.⁴² A professor of epidemiology has argued that this revision had the effect of "seriously" complicating attempts to trace the patterns of lung cancer in this century by "removing a needed safeguard for accuracy":

Primary and secondary lung cancer are separate disease entities, with quite possibly distinct different causes. Since ten percent of all cancers spread to the lung, and since, for nearly twenty years, more deaths were coded in the unspecified than in the primary category, the combination of those two categories seriously confused the lung cancer data.⁴³

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Nonetheless, public health officials and cancer societies, in publicizing lung cancer mortality data, have combined the figures in both categories without any recognition that some or all the cases in the unspecified category may not have been primary lung cancer.⁴⁴ Additional changes in subsequent revisions of the ICD have also been criticized.⁴⁵ As one specialist commented, such changes are "a disturbing influence in the continuity of record-keeping and data-retrieval."⁴⁶

Furthermore, some studies report significant differences among countries in the coding practices for cancer and death certificates. Such differences may, in part, explain variations in cancer mortality reported between countries. For example, researchers who reportedly found such differences among eight countries of the European Economic Community warned that "comparisons of mortality statistics for respiratory diseases between different countries should therefore be viewed with caution."⁴⁷ Similarly, another analysis of such differences asserted that "there is no doubt that such discrepancies explain part of the differences in cause-specific mortality between countries."⁴⁸

Clearly, comparisons of national and international lung cancer mortality trends and cigarette consumption used to support the causal hypothesis are oversimplistic approaches to a complicated problem. Such an approach does not take into account

the numerous shortcomings of the data utilized. Without an appreciation of the difficulties involved, questionable conclusions may be drawn.

Lung Cancer in Women

Reports that lung cancer death rates have been rising rapidly for women are also used as "proof" that increased smoking is responsible. Once again, however, an analysis of the statistical data indicates that this simple assumption may be scientifically inaccurate. For example, the medical university group which suggested that "detection bias" may have distorted the statistical picture regarding cigarette smoking and lung cancer has argued that this may be particularly true for women. They reached that conclusion after observing a dramatic increase in the use of certain diagnostic techniques in female lung cancer patients -- from 52 percent of patients in 1953 to 78 percent by 1964.⁴⁹ They commented that their findings, which suggest that "the current increase of lung cancer in women may arise mainly from improved detection," also "evoke suspicions that cigarette smoking may lead more to the diagnosis of lung cancer than to the disease itself."⁵⁰

In a related study, these researchers speculated that not only "detection bias" but also the increasing role of women in

the workplace may have a significant impact on the validity of lung cancer statistics:

As women have increasingly entered the work force, they may have received an increased exposure to carcinogenic substances; but they have also received increased diagnostic surveillance from health programs associated with industrial employment.⁵¹

Thus, they suggest that even if the increase in women's lung cancer rates is real, other factors besides smoking may be responsible. This viewpoint has also been expressed by others. For example, a Canadian researcher remarked "much more significant than changes in women's smoking habits have been the changes in their employment."⁵²

Other questions about the relationship between lung cancer and smoking in women were raised by a British medical physicist who carefully examined male and female lung cancer mortality patterns in England and Wales over the past century. He reported a "remarkable synchrony in the recorded changes" for both sexes during that time. In other words, even though male lung cancer rates in those countries have always been higher than female rates, the patterns of increase over time in both sexes have been almost exactly the same -- despite the fact that female consumption of cigarettes increased markedly thirty years after the striking rise in male consumption. In his view, if smoking caused this increased

mortality, the female lung cancer mortality pattern should not parallel the male pattern in time; rather, the female pattern should increase sharply about 30 years after the males'. However, he did not observe such differences. He specifically noted that "the most striking sustained rise in the increments of mortality for both sexes covers the period 1916-20 to 1931-35, when cigarette smoking can have made virtually no contribution to the large increase" in the female rate.⁵³

As these examples illustrate, there are numerous difficulties in evaluating the epidemiological studies on smoking and lung cancer. Such difficulties raise serious questions regarding the reliability of the underlying data in such studies.

Biological Mechanism

Demonstration of a mechanism by which normal cells become cancerous is essential in addressing what role, if any, an agent plays in the development of cancer. Although hypotheses and theories frequently appear in the scientific literature, no biological mechanisms have been presented to explain how lung cancer is caused, whether by smoking or by any other factor. Indeed, two scientists have commented, "Although a large number of factors have been associated with the development of malignant neoplasms [cancers] in humans, the mechanisms involved are still largely

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unknown."⁵⁴ Without knowledge of how a factor causes disease, one must conclude it is still a suspect, not an established cause.

Animal Studies

The results of laboratory studies and animal experiments also raise substantial questions about the nature of the relationship between smoking and lung cancer. Animal studies cited in this context have generally used one of two experimental techniques -- inhalation or skin painting. In inhalation studies, test animals are trained to or are forced to inhale cigarette smoke or one or more of its constituents. In skin painting studies, "tar" is painted on the shaved back or ears of test animals over prolonged periods of time. Both techniques are open to scientific criticism. Furthermore, despite the extensive use of these and other techniques, two well-known anti-smoking British researchers conceded that "30 years of laboratory research has yet to identify reliably the important carcinogenic factors in cigarette smoke."⁵⁵

Inhalation Studies

Animal inhalation experiments are generally thought to provide the most relevant experimental data because such experiments come the closest to simulating the human smoking experience. Although many such experiments have been conducted, they have failed

to show that inhalation of fresh whole tobacco smoke causes human-type lung cancer in animals. This failure has been recognized in several U.S. Surgeon General's Reports on Smoking and Health. For example, the 1964 Report stated:

The production of bronchogenic carcinomas [lung cancers] has not been reported by any investigator exposing experimental animals to tobacco smoke.⁵⁶

A similar comment appeared in the 1982 Surgeon General's Report which was the most recent to focus on cancer:

Attempts to induce significant numbers of bronchogenic carcinoma in laboratory animals were negative in spite of major efforts with several species and strains.⁵⁷

The publication, several years later, of the results of a massive inhalation study using thousands of mice reaffirmed the conclusion of the 1982 report. According to the researchers who conducted the study, none of the smoke-exposed mice developed squamous cell carcinoma, the type of lung cancer most generally associated in the epidemiological studies with cigarette smoking. Although some of the animals did develop adenocarcinomas, a type of lung cancer not consistently associated with cigarette smoking, the same cancers occurred in the control animals; there was no statistically significant difference between the two groups.⁵⁸

A few inhalation studies have reported the production of isolated lung cancers. One such experiment, using beagle dogs,⁵⁹ was widely publicized at one time as having provided the conclusive inhalation evidence. However, that study, like the other inhalation studies, has been heavily criticized for its improper experimental design, the experimental procedure followed, and possible misinterpretation of the pathological findings.⁶⁰

Skin Painting Experiments

So-called skin painting experiments prompted a great deal of interest because the tumors which resulted are claimed to be evidence that similar tumors could develop in human lungs from inhaling cigarette smoke. However, it is not appropriate to compare skin painting experiments to the inhalation process of humans. Perhaps the most important reason is that "tar" is an artificially created laboratory product consisting of highly concentrated and physically altered cigarette smoke particulate matter which is gathered either by passing cigarette smoke through a cold trap at extremely cold temperatures or by using filters and a drying process. The substances as found in "tar" are not found in cigarette smoke. That may be why this product is sometimes referred to as condensate.

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In addition, the concentrations of "tar" used in such experiments are extremely high. One researcher has estimated the amounts utilized to be equivalent to an individual smoking over 100,000 cigarettes per day.⁶¹ Furthermore, the skin and ears of laboratory animals are not similar to human lung tissue. Animal skin lacks the intricate clearance mechanisms of the lungs, such as the mucus blanket which coats the lining of the major airways of the lung. Consequently, such experiments have been characterized as applying "the wrong material, in the wrong form, in the wrong concentration, to the wrong tissue of the wrong animal."⁶²

Thus, the animal studies designed to investigate the claimed relationship between smoking and lung cancer do not support either the popular interpretation of the epidemiological evidence or a conclusion of causation. As a knowledgeable observer of research in this area has stated: "Bronchogenic carcinoma has never been produced by tobacco or its products in any experimental animal despite the multiplicity of attempts."⁶³ [Emphasis added] In short, animal studies do not support the claim that cigarette smoking causes lung cancer.

Other Factors

Lung cancer is said to be multifactorial in etiology. That is, many factors may be involved in the development of lung

cancer. For example, in addition to smoking, occupational exposures,⁶⁴ viruses,⁶⁵ diet,⁶⁶ genetic influences,⁶⁷ food additives,⁶⁸ pollution,⁶⁹ depression and stress,⁷⁰ impaired body defense mechanisms,⁷¹ diesel and gasoline exhausts,⁷² and even keeping pet birds⁷³ have been implicated as risk factors.

Occupational exposures in particular have received a great deal of attention as a possible factor in lung cancer development. In fact, researchers with the International Agency for Research on Cancer (IARC) attempted to estimate the fraction of lung cancer cases which may be attributable to occupational exposures. Although they determined that the available published literature is too limited to make such estimates for the general public, they did conclude that the proportion of cases attributable to such exposures "can be very elevated (up to 40%) among selected populations resident in specific areas." In making these estimates, they attempted to take into account the alleged impact of cigarette smoking but concluded that it "does not appear to act consistently as a strong confounder of the association between lung cancer and elevated risks due to the exposure to carcinogens [cancer causing substances] in the working environment."⁷⁴

Despite such reports, many workers are still exposed to industrial agents for which no occupational exposure standards have been established. This problem was recognized by one of the

leading authorities on occupational cancer, who warned that such exposures could continue if public attention was concentrated too strongly on cigarette smoking.⁷⁵ His concerns are shared by others, including an expert in environmental contaminants who has studied these problems for many years:

A real question exists if cigarette smoking is not diverting attention from the effects of occupational exposure on industrial workers⁷⁶

He contends that when both smoking and occupation are considered "it is the occupation -- and not smoking -- that appears to be the major cause of cancer."⁷⁷

Other theories have also been advanced. In the 1950's, the late Sir Ronald Fisher of England, world-famed statistician and geneticist, proposed that "constitutional" factors might be far more important than smoking in lung cancer development.⁷⁸ His hypothesis suggests that some people who have a hereditary predisposition for lung cancer also have a hereditary tendency toward smoking. More recently, a prominent medical physicist, who reviewed much of the literature on smoking and lung cancer, concluded that Fisher's hypothesis still provides the best explanation of the data.⁷⁹

In the past few years, another factor has received considerable attention. Radon is a naturally occurring radioactive gas formed by the disintegration of uranium in the soil. Surveys have shown that indoor concentrations of radon gas and its decay products can be appreciable. Based on studies of uranium miners exposed to radon daughters, it has been asserted that radon may be a significant health risk for residents of homes located in areas with high concentrations of uranium. In the United States, for example, it has been estimated that about 20,000 lung cancer deaths a year may be attributed to radon.⁸⁰ In the United Kingdom, about 5,000 mostly lung cancer deaths are attributed to radon.⁸¹

However, which -- if any -- of these factors plays a role in the causation of lung cancer is as yet undetermined.

Conclusion

Despite claims about smoking and lung cancer, it has not been scientifically established that smoking causes lung cancer. The pathogenesis or development of lung cancer is complex, and an understanding of lung cancer causation continues to elude the scientific community. Basic issues remain unresolved, and much more research is needed to fill the wide gaps in knowledge.

REFERENCES

1. U.S. Department of Health, Education, and Welfare, "Criteria for Judgment," Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service, Public Health Service Publication No. 1103, Washington, D.C., U.S. Government Printing Office, Chapter 3, 17-21 (at 20), 1964.
 2. Hill, A.B., "The Environment and Disease: Association or Causation?" Proceedings of the Royal Society of Medicine 58(5): 295-300 (at 299), 1965.
 3. Burch, P.R.J., "The Surgeon General's 'Epidemiologic Criteria for Causality.' A Critique," Journal of Chronic Diseases 36(12): 821-836 (at 821), 1983.
 4. Burch, P.R.J., "The Surgeon General's 'Epidemiologic Criteria for Causality.' A Critique," Journal of Chronic Diseases 36(12): 821-836 (at 823), 1983.
 5. Burch, P.R.J., "The Surgeon General's 'Epidemiologic Criteria For Causality.' Reply to Lilienfeld," Journal of Chronic Diseases 37(2): 148-156 (at 151), 1984.
 6. Berkson, J., "Smoking and Cancer of the Lung," Proceedings of the Staff Meetings of the Mayo Clinic 35: 367-385 (at 2 of reprint), 1960.
 7. Hill, G., "Smoking and Lung Cancer," Archives of Internal Medicine 148: 2538-2539 (at 2539), December, 1988.
 8. Rigdon, R.H. and Kirchoff, H., "Cancer of the Lung From 1900 to 1930," Surgery, Gynecology & Obstetrics 107: 105-118, August, 1958.
 9. Rosenblatt, M.B., "Cancer of the Lung: Facts and Fallacies," Journal of the Kentucky Medical Association 56(2): 131-136 (at 132), February, 1958.
 10. Burch, P.R.J., "The Surgeon General's 'Epidemiologic Criteria for Causality.' A Critique," Journal of Chronic Diseases 36(12): 821-836, December, 1983.
- U.S. Department of Health and Human Services, The Health Consequences of Smoking: Cancer. A Report of the Surgeon General: 1982, DHHS Publication No. (PHS) 82-50179, Washington, D.C., U.S. Government Printing Office, 44, 1982.

11. Rigdon, R.H., "The Smoking Controversy," Journal of the American Medical Association 173(3): 293-295, May 21, 1960.
- Herrold, K., "Survey of Histologic Types of Primary Lung Cancer in U.S. Veterans," Pathology Annual 7: 45-79, 1972.
- Miller, A.B., "Epidemiology: Problems in the Study of Cancers of Low Incidence and the Need for Collaboration," Journal of the National Cancer Institute 54(2): 299-301, February, 1975.
- Hehlmann, R., "Psychosomatik und Krebs (Psychosomatics and Cancer)," Münchener medizinische Wochenschrift 124(38): 829-830, September 24, 1982. Translation.
12. Macdonald, E.J., Lichtenstein, H., Nooner, D., Flory, D., Wikstrom, S. and Oro, J., "Epidemiological Factors in Lung Cancer Among Women in El Paso County, Texas, 1944-1969," Journal of the American Medical Womens Association 28(9): 459-467, 1973.
- Enstrom, J.E., "Rising Lung Cancer Mortality Among Nonsmokers," Journal of the National Cancer Institute 62(4): 755-760, 1979.
- Schneiderman, M.A., Davis, D.L. and Wagener, D.K., "Lung Cancer That is Not Attributable to Smoking," Journal of the American Medical Association 261(18): 2635-2636, May 12, 1989.
- Koo, L.C. and Ho, J.H-C., "Worldwide Epidemiological Patterns of Lung Cancer in Nonsmokers," International Journal of Epidemiology 19(3): S14-S23 (Supplement 1), 1990.
13. Sadowsky, D.A., Gilliam, A.G. and Cornfield, J., "The Statistical Association Between Smoking and Carcinoma of the Lung," Journal of the National Cancer Institute 13: 1237-1258, 1953.
- Passey, R.D., "Neoplasia: Lungs." In: Tobacco and Health. G. James and T. Rosenthal (eds.), Springfield, Ill., Charles C. Thomas, Chapter 9, 105-122, 1962.
- Poche, R., Mittmann, O. and Kneller, O., "Statistische Untersuchungen über das Bronchialcarcinom in Nordrhein Westfalen (Statistical Studies of Bronchial Carcinoma in the North Rhine Westphalia State)," Zeitschrift für Krebsforschung 66: 87-108, 1964. Translation.
- Buechley, R.W., "Smoking and Lung Cancer: Further Evidence on a Proposition By Professor Passey," Lancet 2: 35-36, July 4, 1964.

2025500153

Herrold, K.M., "Survey of Histologic Types of Primary Lung Cancer in U.S. Veterans, Pathology Annual 7: 45-79, 1972.

McDuffie, H.H., Klaassen, D.J., Dosman, J.A., "Characteristics of Patients With Primary Lung Cancer Diagnosed at Age 50 Years or Younger," Chest 96(6): 1298-1301, December, 1989.

14. Burch, P.R.J., "Smoking and Cancer," Lancet 1(7815): 1315-1316, June 9, 1973.

15. Hinds, M.W., Kolonel, L.N., Lee, J. and Hirohata, T., "Associations Between Cancer Incidence and Alcohol/Cigarette Consumption Among Five Ethnic Groups in Hawaii," British Journal of Cancer 41: 929-940, 1980.

Hinds, M.W., Stemmermann, G.N., Yang, H.-Y., Kolonel, L.N., Lee, J. and Wegner, E., "Differences in Lung Cancer Risk From Smoking Among Japanese, Chinese and Hawaiian Women in Hawaii," International Journal of Cancer 27: 297-302, 1981.

16. Koo, L.C., Ho, J.H.-C. and Saw, D., "Active and Passive Smoking Among Female Lung Cancer Patients and Controls in Hong Kong," Journal of Experimental and Clinical Cancer Research 4(2): 367-375, October - December, 1983.

17. Burch, P.R.J., "Smoking and Lung Cancer: The Problem of Inferring Cause (With Discussion)," Journal of the Royal Statistical Society Series A (General) 141(Part 4): 437-477, 1978.

18. Doll, R. and Hill, A.B., "A Study of the Aetiology of Carcinoma of the Lung," British Medical Journal 2: 1271-1286, December 13, 1952.

Fischer, R., In: Smoking: The Cancer Controversy. Some Attempts to Assess the Evidence, Edinburgh, Oliver and Boyd, 1959.

Doll, R. and Peto, R., "Mortality in Relation to Smoking: 20 Years' Observations on Male British Doctors," British Medical Journal 2: 1525-1536, December 25, 1976.

Burch, P.R.J., "Smoking and Health," British Medical Journal 1(6054): 165, 1977.

Higenbottam, T., Shipley, M.J. and Rose, G., "Cigarettes, Lung Cancer, and Coronary Heart Disease: The Effects of Inhalation and Tar Yield," Journal of Epidemiology and Community Health 36: 113-117, 1982.

19. Langston, H.T., Statement, Re: "Comprehensive Smoking Prevention Education Act - Appendix." In: Hearings Before the Committee on Energy and Commerce, Subcommittee on Health and the Environment, United States House of Representatives, Ninety-Seventh Congress, Second Session, 657-663, March 5, 11, 12, 1982.
 20. Rosenblatt, M.B., "The Increase in Lung Cancer: Epidemic or Artifact?," Medical Counterpoint 1(1): 29-33, 37-39 (at 38), March, 1969.
 21. McFarlane, M.J., Feinstein, A.R., Wells, C.K. and Chan, C.K., "The 'Epidemiologic Necropsy': Unexpected Detections, Demographic Selections, and Changing Rates of Lung Cancer," Journal of the American Medical Association 258(3): 331-338, July 17, 1987.
 22. Rosenblatt, M., Statement, Re: "Cigarette Labeling and Advertising -- 1969." In: Hearings Before the Committee on Interstate and Foreign Commerce, United States, House of Representatives, Ninety-First Congress, First Session, 1255-1263, April 15-30 and May 1, 1969.
 23. Rosenblatt, M.B., "The Increase in Lung Cancer: Epidemic or Artifact?," Medical Counterpoint: 29-33, 36-39 (at 36), March, 1969.
 24. Bankl, H. and Krepler, R., "Das Klinisch Fehldiagnostizierte Karzinom (Untersuchungen am Obduktionsgut) [Clinically Misdiagnosed Carcinoma (Investigation of Autopsy Reports)]," Wiener Klinische Wochenschrift 83(1): 1-5, January 8, 1971. Translation.
- Hiyoshi, Y., et al., "Malignant Neoplasms Found By Autopsy in Hisayama, Japan, During the First Ten Years of a Community Study," Journal of the National Cancer Institute 59(1): 13-19, July, 1977.
- Sherwin, R.P., "The Differentiation of Primary Lung Cancer From Metastatic Disease." In: Pulmonary Metastasis. L. Weiss and H.A. Gilbert (eds.). Boston, G.K. Hall & Co., Chapter 7, 91-98, 1978.
- Hill, C.A., "Thoracic Tuberculosis, Mycobacteriosis, MEROsis, and BCGosis in a Cancer Treatment Center," Radiology 153(2): 311-316, November, 1984.
- Miller, W.T., "Pulmonary Tuberculosis: The Spectrum of Radiographic Findings," Medical Times 113(1): 56-63, 67-69, January, 1985.

2025500155

Peuchot, M. and Libshitz, H.I., "Pulmonary Metastatic Disease: Radiologic-Surgical Correlation," Radiology 164(3): 719-722, 1987.

Mericka, O., Zatloukal, P. and Bohut, V., "Plicní tuberkulóza imitující bronchogenní karcinom (Pulmonary Tuberculosis Imitating Bronchogenic Carcinoma)," Studia Pneumologica et Phthiseologica Cechoslovaca 47(6): 376-379, June, 1987. Translation.

25. Rosenblatt, M.B., Teng, P.K., Kerpe, S. and Beck, I., "Causes of Death in 1,000 Consecutive Autopsies," New York State Journal of Medicine 71(18): 2189-2193, September 15, 1971.

Rosenblatt, M.B., Teng, P., Kerpe, S., and Beck, I., "Prevalence of Lung Cancer: Disparity Between Clinical and Autopsy Certification," Medical Counterpoint 3(10): 53-54, 56-59, 63, October, 1971.

Rosenblatt, M.B., Teng, P.K. and Kerpe, S., "Diagnostic Accuracy in Cancer as Determined By Post Mortem Examination," Progress in Clinical Cancer V: 71-80, 1973.

26. McFarlane, M.J., Feinstein, A.R. and Wells, C.K., "Necropsy Evidence of Detection Bias in the Diagnosis of Lung Cancer," Archives of Internal Medicine 146(9): 1695-1698, September, 1986.

Wells, C.K. and Feinstein, A.R., "Detection Bias in the Diagnostic Pursuit of Lung Cancer," American Journal of Epidemiology 128(5): 1016-1026, 1988.

27. McFarlane, M.J., Feinstein, A.R. and Wells, C.K., "Necropsy Evidence of Detection Bias in the Diagnosis of Lung Cancer," Archives of Internal Medicine 146(9): 1695-1698 (at 1698), September, 1986.

28. Burch, P., "Smoking and Health," British Medical Journal I: 165, January 15, 1977.

29. King, D.W., "Potential of the Autopsy," Archives of Pathology and Laboratory Medicine 108(6): 439-443 (at 442), June, 1984.

30. King, D.W., "Potential of the Autopsy," Archives of Pathology and Laboratory Medicine 108(6): 439-443 (at 442), June, 1984.

Carter, J.R., "The Problematic Death Certificate," New England Journal of Medicine 313(20): 1285-1286 (at 1285), November 14, 1985.

2025500156

31. Rosenblatt, M.B., Teng, P., Kerpe, S., and Beck, I., "Prevalence of Lung Cancer: Disparity Between Clinical and Autopsy Certification," Medical Counterpoint 3(10): 53-54, 56-59, 63, October, 1971.
- Rosenblatt, M.B., Teng, P.K., Kerpe, S. and Beck, I., "Causes of Death in 1,000 Consecutive Autopsies," New York State Journal of Medicine 71(18): 2189-2193, September 15, 1971.
- Rosenblatt, M.B., Teng, P.K. and Kerpe, S., "Diagnostic Accuracy in Cancer as Determined By Post Mortem Examination," Progress in Clinical Cancer V: 71-80, 1973.
32. Bauer, F.W. and Robbins, S.L., "An Autopsy Study of Cancer Patients. I. Accuracy of the Clinical Diagnoses (1955 to 1965) Boston City Hospital," Journal of the American Medical Association 221(13): 1471-1474, September 25, 1972.
33. Ehrlich, D., Li-Sik, M. and Modan, B., "Some Factors Affecting the Accuracy of Cancer Diagnosis," Journal of Chronic Diseases 28(7/8): 359-364, 1975.
34. Stenback, F. and Paivarinta, H., "Relation Between Clinical and Autopsy Diagnoses, Especially as Regards Cancer," Scandinavian Journal of Social Medicine 8(2): 67-72, 1980.
35. Cameron, H.M. and McGoogan, E., "A Prospective Study of 1152 Hospital Autopsies: II. Analysis of Inaccuracies in Clinical Diagnoses and Their Significance," Journal of Pathology 133(4): 285-300, 1981.
36. Jimenez, F., Teng, P. and Rosenblatt, M.B., "Cancer of the Lung in Males," Bulletin of the New York Academy of Medicine 51(3): 432-438, March, 1975.
37. Gittelsohn, A. and Senning, J., "Studies on the Reliability of Vital and Health Records: 1. Comparison of Cause of Death and Hospital Record Diagnoses," American Journal of Public Health 69(7): 680-689, July, 1979.
38. Gwynne, J., "Death Certification in Dunedin Hospitals," New Zealand Medical Journal 86(592): 77-81, July 27, 1977.
39. Kirchner, T., Nelson, J. and Burdo, H., "The Autopsy as a Measure of Accuracy of the Death Certificate," New England Journal of Medicine 313(20): 1263-1269 (at 1267), November 14, 1985.

2025500157

40. Rosenblatt, M.B., "Cancer of the Lung: Facts and Fallacies," Journal of the Kentucky Medical Association 56(2): 131-136, February, 1958.
- Oeser, H. and Koeppe, P., "Lungenkrebs - in statischer Sicht (Lung Cancer - From the Statistical Aspects)," Öffentliche Gesundheitswesen 42(9): 590-598, 1980. Translation.
- Lock, W., "Epidemiologie der Krebserkrankung - 105 Jahre Mortalitätsstatistik (Epidemiology of Carcinosis: 105 Years of Mortality Statistics)," Münchener medizinische Wochenschrift 123(40): 1491-1497, October 2, 1981. Translation.
- Payne, M., Cohen, P. and Dix, D., "The Role of Aging in Cancer Incidence: Interpretation of the Lung Cancer Anomaly," Clinical Research 32(3): 707A, September, 1984.
- Rainsford, J., Cohen, P. and Dix, D., "On the Role of Aging in Cancer Incidence: Analysis of the Lung Cancer Data," Anticancer Research 5(4): 427-430, July-August, 1985.
- Gori, G.B. and Lynch, C.J., "Decline of U.S. Cancer Mortality Rates: Expert Estimates of Past Underreporting," Regulatory Toxicology and Pharmacology 6(3): 261-273, 1986.
41. Macdonald, E.J., Statement, Re: "Comprehensive Smoking Prevention Education Act -- Appendix." In: Hearings Before the Committee on Energy and Commerce, Subcommittee on Health and the Environment, United States Senate, Ninety-Seventh Congress, Second Session, 669-684, March 5, 11, 12, 1982.
42. Israel, R.A. and Klebba, A.J., "A Preliminary Report on the Effect of Eighth Revision ICDA on Cause of Death Statistics," American Journal of Public Health 59(9): 1651-1660, September, 1969.
- Percy, C., Garfinkel, L., Krueger, D.E. and Dolman, A.B., "Apparent Changes in Cancer Mortality, 1968," Public Health Reports 89(5): 418-428, September-October, 1974.
43. Macdonald, E.J., Statement, Re: "Comprehensive Smoking Prevention Education Act -- Appendix." In: Hearings Before the Committee on Energy and Commerce, Subcommittee on Health and the Environment, United States, House of Representatives, Ninety-Seventh Congress, Second Session, 669-684, March 5, 11, 12, 1982.
44. Rosenblatt, M.B., "The Increase in Lung Cancer: Epidemic or Artifact,?" Medical Counterpoint: 29-33, 36-39, March, 1969.

2025500158

Rosenblatt, M., Statement, Re: "Cigarette Labeling and Advertising -- 1969." In: Hearings Before the Committee on Interstate and Foreign Commerce, United States, House of Representatives, Ninety-First Congress, First Session, 1255-1263, April 15-30 and May 1, 1969.

45. Manton, K.G. and Stallard, E., "Mortality Data: Concepts and Data Quality Issues." In: Recent Trends in Mortality Analysis. New York, Academic Press, Inc., Chapter 2, 11-43, 1984.
46. Kurtzke, J.F., "Reviews and Commentary. ICD9: A Regression," American Journal of Epidemiology 109(4): 383-393, April, 1979.
47. Kelson, M.C. and Heller, R.F., "The Effect of Death Certification and Coding Practices on Observed Differences in Respiratory Disease Mortality in 8 E.E.C. Countries," Revue D Epidemiologie Et De Sante Publique 31(4): 423-432 (at 424), 1983.
48. Brzezinski, Z.J., "Mortality Indicators and Health-For-All Strategies in the WHO European Region," World Health Statistics Quarterly 39(4): 365-378, 1986.
49. "Smoking Link to Lung Ca Termed Diagnostic Bias," Family Practice News, July 15, 1974.

Feinstein, A. and C. Wells, "Cigarette Smoking and Lung Cancer: The Problems of 'Detection Bias' in Epidemiologic Rates of Disease," Transactions of the Association of American Physicians 87: 180-185, 1974.
50. Feinstein, A. and C. Wells, "Cigarette Smoking and Lung Cancer: The Problems of 'Detection Bias' in Epidemiologic Rates of Disease," Clinical Research 22(3): 535A, April, 1974.
51. McFarlane, M.J., Feinstein, A.R., Wells, C.K. and Chan, C.K., "The 'Epidemiologic Necropsy': Unexpected Detections, Demographic Selections, and Changing Rates of Lung Cancer," Journal of the American Medical Association 258(3): 331-338 (at 335-336), July 17, 1987.
52. Sterling, T., "Additional Comments on the Critical Assessment of the Evidence Bearing on Smoking as the Cause of Lung Cancer," American Journal of Public Health 66(2): 161-164 (at 162), February, 1976.
53. Burch, P.R.J., "Smoking and Lung Cancer: The Problem of Inferring Cause (With Discussion)," Journal of the Royal Statistical Society, Series A (General): 141(Part 4): 437-

477 (at 444-445), 1978.

54. Albanes, D. and Winick, M., "Are Cell Number and Cell Proliferation Risk Factors for Cancer?," Journal of the National Cancer Institute 80(10): 772-775 (at 772), July 20, 1988.
55. Doll, R. and Peto, R., "The Control of Lung Cancer," New Scientist 105(1440): 26-30 (at 28), January 24, 1985.
56. U.S. Department of Health, Education, and Welfare, "Experimental Pulmonary Carcinogenesis: Attempts to Induce Lung Cancer With Tobacco and Tobacco Smoke," Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service, Public Health Service Publication No. 1103, Washington, D.C., U.S. Government Printing Office, 165, 1964.
57. U.S. Public Health Service, Office on Smoking and Health, "Mechanisms of Carcinogenesis," The Health Consequences of Smoking: Cancer. A Report of the Surgeon General: 1982, Department of Health and Human Services, Washington, D.C., U.S. Government Printing Office, DHHS Publication No. (PHS) 82-50179, Part III, 171-235 (at 218), 1982.
58. Henry, C.J. and Kouri, R.E., Chronic Exposure of Mice to Cigarette Smoke, Microbiological Associates, New York, Field, Rich and Associates, Inc., 1984.

Henry, C.J. and Kouri, R.E., "Chronic Inhalation Studies in Mice. II. Effects of Long-Term Exposure to 2R1 Cigarette Smoke on (C57BL/Cum x C3H/AnfCum)F₁ Mice," Journal of the National Cancer Institute 77(1): 203-212, July, 1986.
59. Hammond, E.C., Auerbach, O., Kirman, D. and Garfinkel, L., "Effects of Cigarette Smoking on Dogs. I. Design of Experiment, Mortality, and Findings in Lung Parenchyma," Archives of Environmental Health 21: 740-753, December, 1970.

Auerbach, O., Hammond, E.C., Kirman, D. and Garfinkel, L., "Effects of Cigarette Smoking on Dogs. II. Pulmonary Neoplasms," Archives of Environmental Health 21: 754-768, December, 1970.
60. National Academy of Sciences, Committee on Biologic Effects of Atmospheric Pollutants, "Characteristics of Human Disease Related to Polycyclic Organic Matter." In: Biologic Effects of Atmospheric Pollutants: Particulate Polycyclic Organic Matter. Washington, D.C., National Academy of Sciences, Chapter 16, 172-190, 1972.

Feinstein, , A.R., "Clinical Biostatistics. XIX. Ambiguity and Abuse in the Twelve Different Concepts of 'Control,'" Clinical Pharmacology and Therapeutics 14(1): 112-122, 1973.

Louis, C.J., Blunck, J.M. and Richmond, L.M., "Agarose-Gel Electrophoresis of Soluble Proteins From Bronchial Mucosa and Bronchogenic Carcinoma," Oncology 27: 324-335, 1973.

Hirth, R.S. and Hottendorf, G.H., "Lesions Produced by a New Lungworm in Beagle Dogs," Veterinary Pathology 10: 385-407, 1973.

Binns, R., "Animal Inhalation Studies With Tobacco Smoke (A Review)," Review of Environmental Health 2(8): 81-116, 1975.

Dijkstra, B.K.S., "Origin of Carcinoma of the Bronchus. Part I: The Smoking Hypothesis," South African Cancer Bulletin 21(1): 7-16, January/March, 1977.

Abraham, J.L., "Talc Pneumoconiosis in Cigarette Smoking Dogs," American Review of Respiratory Diseases 119(4, Part 2): 197, April, 1979.

61. MacDonald, I., Statement, Re: "False and Misleading Advertising (Filter-Tip Cigarettes)." In: Hearings Before the Committee on Government Operations, Legal and Monetary Affairs Subcommittee, United States Senate, Eighty-Fifth Congress, First Session, 224-240, July 18-19, 23-26, 1957.
62. Hockett, R., "Where Do We Go From Here in Tobacco and Health Research?," Presentation Before the Burley and Dark Leaf Tobacco Export Association, Lexington, Kentucky, October 2, 1967 (at p. 11).

Hockett, R.C., Statement, Re: "Public Health Cigarette Amendments of 1971." In: Hearings Before the Committee on Commerce, Consumer Subcommittee, United States Senate, Ninety-Second Congress, Second Session, 97-123, February 1, 3, and 10, 1972.
63. Hockett, R.C., Statement, Re: "Smoking Prevention Education Act." In: Hearings Before the Committee on Energy and Commerce, Subcommittee on Health and the Environment, United States House of Representatives, Ninety-Eighth Congress, First Session, 841-851 (at 844), March 9, 17, 1983.
64. Reniers, J. and Meheus, A., "Een Proportionele Sterftestudie In Een Antwerpse Draadtrekkerij (A Proportional Mortality Study in an Antwerp Steel Wire Plant)," Tijdschrift voor

Sociale Gezondheidszorg 65(4): 96-98, 1987. Translation.

Magnani, C., Terracini, B., Bertolone, G.P., Castagneto, B., Cocito, V., De Giovanni, D., Paglieri, P. and Botta, M., "Mortalità per Tumori E Altre Malattie Del Sistema Respiratorio Tra I Lavoratori Del Cemento-Amianto A Casale Monferrato. Uno Studio Di Coorte Storico (Mortality From Cancer and Other Diseases of the Respiratory Apparatus Among Asbestos Cement Workers in Casale Monferrato (Italy): Historical Cohort Study)," La Medicina Del Lavoro 78(6): 441-452, November-December, 1987. Translation.

Wall, S., Taube, A. and A. Sandstrom, "Fallet Rönnskär: Historik, arbetsmiljö, överdödlighet (Epidemiology at a Smelter (I): The Rönnskär Case: History, Occupational Environment, Excess Mortality)," Läkartidningen 85(21): 1889-1893, May 25, 1988. Translation.

Sandstrom, A., Wall, S. and Taube, A., "Fallet Rönnskär: Hur gick det sedan? (Epidemiology at a Smelter (II): The Rönnskär Case: What Happened Later?)," Läkartidningen 85(21): 1896-1899, 1988. Translation.

Esaki, H. and Maeda, M., "Mortality Among Migrant Tunnel Workers," Japanese Journal of Industrial Health 30(6): 481-485, November, 1988.

Une, H., Esaki, H., and Maeda, M., "Mortality Among Migrant Tunnel Workers," Japanese Journal of Industrial Health 30(6): 481-485, November, 1988.

Hansen, E.S., "Cancer Incidence in an Occupational Cohort Exposed to Bitumen Fumes," Scandinavian Journal of Work, Environment and Health 15(2): 101-105, April, 1989.

Sitas, F., Douglas A.J. and Webster, E.C., "Respiratory Disease Mortality Patterns Among South African Iron Moulders," British Journal of Industrial Medicine 46: 310-315, May, 1989.

Guenel, P., Hojberg, G. and Lynge, E., "Cancer Incidence Among Danish Stone Workers," Scandinavian Journal of Work, Environment and Health 15(4): 265-270, August, 1989.

Hours, M., Cardis, E., Marciniak, A., Quelin, P. and Fabry, J., "Mortality of a Cohort in a Polyamide-Polyester Factory in Lyon: A Further Follow Up," British Journal of Industrial Medicine 46(9): 665-670, September, 1989.

Forastiere, F., Lagorio, S., Michelozzi, P., Perucci, C.A. and Axelson, O., "Mortality Pattern of Silicotic Subjects in

2025500162

the Latium Region, Italy," British Journal of Industrial Medicine 46(12): 877-880, December, 1989.

Kawachi, I., Pearce, N. and Fraser, J., "A New Zealand Cancer Registry-Based Study on Cancer in Wood Workers," Cancer 64(12): 2609-2613, December 15, 1989.

65. Chang, L.W., Menna, J.H., Wang, P.M., Kalderon, A.E., Sorenson, J.R.J. and Wennerstrom, D.E., "The Potential Oncogenic Activity of Influenza A Virus in Lungs of Mice," Experimental Pathology 25(4): 223-231, 1984.

Franco, R., Stanislawski, E., Barrios, R., Oliva, E. and Fortoul, T., "Ultrastructural Features in Bronchiolo-Alveolar Carcinoma With Emphasis in the Virus-Like Nuclear Inclusions," American Review of Respiratory Diseases Supplement 131 (4, Part 2): A116, 1985.

Bezuglova, T.V., Lange, A., Gusman, B.S. and Ritter, E., "Development of Lung Tumors in Syrian Hamsters After Mixed Infection With Mycoplasma-pneumoniae and Influenza Virus," Bulletin of Experimental and Biological Medicine 99 (4): 508-510, April, 1985.

Kahn, T. and zur Hausen, H., "Zur Ätiologie des Bronchialkarzinoms (The Viral Etiology of Bronchial Carcinoma)," Atemwegs-und Lungenkrankheiten 12(10): 478-481, October, 1986. Translation.

Byrne, J.C., Tsao, M.-S., Fraser, R.S. and Howley, P.M., "Human Papillomavirus-11 DNA in a Patient With Chronic Laryngotracheobronchial Papillomatosis and Metastatic Squamous-Cell Carcinoma of the Lung," New England Journal of Medicine 317(14): 873-878, October 1, 1987.

66. Correa, P., Fontham, E., Chen, V., Craig, J.F., Falk, R. and Pickle, L.W., "Diet, Nutrition, and Cancer," Journal of the Louisiana State Medical Society 140(4): 43-49, April, 1988.

National Research Council, Committee on Diet and Health, "Fat-Soluble Vitamins." In: Diet and Health: Implications for Reducing Chronic Disease Risk. Washington, D.C., National Academy Press, Chapter 11, 311-327, 1989.

Connett, J.E., Kuller, L.H., Kjelsberg, M.O., Polk, B.F., Collins, G., Rider, A. and Hulley, S.B., "Relationship Between Carotenoids and Cancer: The Multiple Risk Factor Intervention Trial (MRFIT) Study," Cancer 64(1): 126-134, July 1, 1989.

Fraser, G.E., Beeson, L. and Phillips, R.L., "Diet and Lung

2025500163

Cancer in Seventh-Day Adventists," American Journal of Epidemiology 130(4): 840-841, October, 1989.

67. Pero, R.W., Johnson, D.B., Markowitz, M., Doyle, G., Lund-Pero, M., Seidegard, J., Halper, M. and Miller, D.G., "DNA Repair Synthesis in Individuals With and Without a Family History of Cancer," Carcinogenesis 10(4): 693-697, April, 1989.
68. Felton, J.S., Knize, M.G., Shen, N.H., Lewis, P.R., Andresen, B.D., Happe, J. and Hatch, F.T., "The Isolation and Identification of a New Mutagen From Fried Ground Beef: 2-Amino-1-Methyl-6-Phenylimidazo[4,5-b]pyridine (PhIP)," Carcinogenesis 7(7): 1081-1086, 1986.
69. Minowa, M., "Local Environmental Factors Associated With Lung Cancer Mortality," Journal of Medicine Soc. Toho University 34(3-4): 252-271, 1987. Translation.

Mumford, J.L., Chapman, R.S., Harris, D.B., He, X.Z., Cao, S.R., Xian, Y.L. and Li, X.M., "Indoor Air Exposure to Coal and Wood Combustion Emissions Associated With a High Lung Cancer Rate in Xuan Wei, China," Environment International 15(1-6): 315-320, 1989.
70. Horne, R.L. and Picard, R.S., "Psychosocial Risk Factors For Lung Cancer," Psychosomatic Medicine 41(7): 503-514, November, 1979.

Shekelle, R.B., Raynor, W.J., Jr., Ostfeld, A.M., Garron, D.C., Bieliauskas, L.A., Liu, S.C., Maliza, C. and Paul, O., "Psychological Depression and 17-Year Risk of Death From Cancer," Psychosomatic Medicine 43(2): 117-125, April, 1981.

Grossarth-Maticek, R., Kanazir, D.T., Schmidt, P. and Vetter, H., "Psychosocial and Organic Variables as Predictors of Lung Cancer, Cardiac Infarct and Apoplexy -- Some Differential Predictors," Personality and Individual Differences 6(3): 313-321, 1985.

Tecoma, E.S. and Huey, L.Y., "Minireview: Psychic Distress and the Immune Response," Life Sciences 36: 1799-1812, 1985.

Kiecolt-Glaser, J.K. and Glaser, R., "Psychological Influences on Immunity," Psychosomatics 27(9): 621-624, September, 1986.

Persky, V.W., Kempthorne-Rawson, J. and Shekelle, R.B., "Personality and Risk of Cancer: 20-Year Follow-Up of the Western Electric Study," Psychosomatic Medicine 49: 435-449, 1987.

2025500164

71. Moszyczynski, P. and Lisiewicz, J., "Deficiency of N-Acetyl-Beta-D-Glucosaminidase in Neutrophils of Cancer Patients," Journal of Cancer Research and Clinical Oncology 108(2): 243-245, 1984.
72. Fraser, D., "Lung Cancer Risk and Diesel Exhaust Exposure," Public Health Review 14(2): 139-171, 1986.
- Siemiatycki, J., Dewar, R., Nadon, L., Gerin, M., Richardson, L. and Wacholder, S., "Associations Between Several Sites of Cancer and Twelve Petroleum-Derived Liquids: Results From a Case-Referent Study in Montreal," Scandinavian Journal of Work, Environment and Health, 13(6): 493-504, December, 1987.
- Siemiatycki, J., Gerin, M., Stewart, P., Nadon, L., Dewar, R. and Richardson, L., "Associations Between Several Sites of Cancer and Ten Types of Exhaust and Combustion Products: Results From a Case-Referent Study in Montreal," Scandinavian Journal of Work, Environment and Health 14(2): 79-90, April, 1988.
- Hayes, R.B., Thomas, T., Silverman, D.T., Vineis, P., Blot, W.J., Mason, T.J., Pickle, L.W., Correa, P., Fontham, T.H. and Schoenberg, J.B., "Lung Cancer In Motor Exhaust-Related Occupations," American Journal of Industrial Medicine 16(6): 685-695, 1989.
73. Holst, P.A., Kromhout D., and Brand, R., "For Debate: Pet Birds as an Independent Risk Factor for Lung Cancer," British Medical Journal 297(6659): 1319-1321, November 19, 1988.
74. Simonato, L., Vineis, P. and Fletcher, A.C., "Estimates of the Proportion of Lung Cancer Attributable to Occupational Exposure," Carcinogenesis 9(7): 1159-1165 (at 1164), 1988.
75. Hueper, W.C, "Lung Cancer and Smoking In Perspective," Lawyers' Medical Cyclopedia . . . of Personal Injuries and Allied Specialties, Revised Volume V, Part A, C.J. Frankel and R.M. Patterson (eds.), Indianapolis, The Allen Smith Company, 559-567, 1972.
76. Sterling, T., "Air Pollution and Smoking," Environment 15(6): 3, July/August, 1973.
77. Sterling, T., "'Does Smoking Kill Workers or Working Kill Smokers? or the Mutual Relationship Between Smoking, Occupation, and Respiratory Disease," International Journal of Health Services 8(3): 437-452 (at 440), 1978.

2025500165

78. Fisher, R., In: Smoking: The Cancer Controversy. Some Attempts to Assess the Evidence, Edinburgh, Oliver and Boyd, 1959.
79. Burch, P.R.J., "Smoking and Lung Cancer: The Problem of Inferring Cause (With Discussion)," Journal of the Royal Statistical Society. Series A (General) 141(Part 4): 437-477, 1978.
80. Hanson, D.J., "Radon Tagged as Cancer Hazard By Most Studies, Researchers," Chemical Engineering News 67(6): 7-13, February 6, 1989.
81. Hughes, J.S., Shaw, K.B. and O'Riordan, M.C., Radiation Exposure of the U.K. Population - 1988 Review, National Radiological Protection Board, NRPB-R227, London, Her Majesty's Stationery Office, March, 1989.

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LUNG CANCER:

CLAIMS/RESPONSES

CLAIM: The statistical evidence against smoking is so strong that no doubt remains about its harmful effect on health.

RESPONSE: One thing that can be said for certain about smoking is that it produces statistics. But, as many have emphasized, statistics can be used to "prove" just about anything. However, statistical associations alone can never prove cause-and-effect relationships; they simply provide leads for further research.¹

In addition, the statistical studies on smoking and health have been challenged scientifically. Many of the population studies from which those statistical associations are reported have been criticized as being seriously flawed in their methodology and reliability of information. For example, many have relied on death certificates for information on causes of death, but numerous studies have reported that death certificates contain inaccurate information.² Such errors can arise where, for example, an individual is diagnosed as having lung cancer but at autopsy is found to have had a primary cancer in another site, for example the kidney, that metastasized or spread to the lung. If the death

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certificate is not revised to reflect the results of the autopsy but instead retains the initial diagnosis, which has been shown to occur, then that incorrect information will be used in future studies.

Furthermore, many of these statistical studies have failed to take into account numerous other factors that have been associated with lung cancer in addition to smoking, such as lifestyle, genetic and inherited traits, occupational and environmental exposures, and psychological variables.³

Finally, the reported "epidemic" of deaths attributed to smoking may be in part artifactual and misleading. Because diagnostic techniques have greatly improved over the last 50 years with the development of such tools as the x-ray and the bronchoscopy, many cases of diseases such as lung cancer are diagnosed today which were either missed or misdiagnosed earlier.⁴ Thus, the "epidemic" may reflect dramatic medical progress. As the world's population grows in size, life expectancy has generally increased markedly. This is significant because many diseases associated with smoking are also frequently diseases of old age.

REFERENCES

1. Furst, A., "A New Look at Arsenic Carcinogenesis." In: Arsenic: Industrial, Biomedical, Environmental Perspectives. W.H. Lederer and R.J. Fensterheim (eds.), New York, Van Nostrand Reinhold Co., Chapter 13, 151-165, 1983.

MacRae, K.D., "What Epidemiological Studies Can Tell Us," Journal of Obstetrics and Gynecology 4(Suppl. 2): S79-S87, 1984.

Barr, J.T., "The Calculation and Use of Carcinogenic Potency: A Review," Regulatory Toxicology and Pharmacology 5(4): 432-459, 1985.
2. Rosenblatt, M.B., Teng, P.K., Kerpe, S., and Beck, I., "Prevalence of Lung Cancer: Disparity Between Clinical and Autopsy Certification," Medical Counterpoint 3(10): 53-54, 56-59, 63, October, 1971.

Rosenblatt, M.B., Teng, P.K., Kerpe, S., and Beck, I., "Diagnostic Accuracy in Cancer as Determined By Post Mortem Examination," Progress in Clinical Cancer 5: 71-80, 1973.

Hoppe, R., "Uber die Lungenkrebsdiagnostik [Diagnosing Lung Cancer], Deutsche medizinische Wochenschrift 102(43): 1565-1566, 1977. Translation.

Medical Services Study Group of the Royal College of Physicians of London, "Death Certification and Epidemiological Research," British Medical Journal II: 1063-1065, 1978.
3. Abse, D.W., Brown, R.S., Buxton, W.D., Demars, J.-P., Kirschner, L.G., Van De Castle, R.L. and Wilkins, M.M., "Personality and Behavioral Characteristics of Lung Cancer Patients," Journal of Psychosomatic Research 18(2): 101-113, 1974.

Macdonald, E., "Air Pollution, Demography, Cancer: Houston, Texas," Journal of the American Medical Women's Association 31(10): 379-395, October, 1976.

Sterling, T., "Does Smoking Kill Workers or Working Kill Smokers? Or The Mutual Relationship Between Smoking, Occupation, and Respiratory Disease," International Journal of Health Services 8(3): 437-452, 1978.

Horne, R.L. and Picard, R.S., "Psychosocial Risk Factors For Lung Cancer," Psychosomatic Medicine 41(7): 503-514, November, 1979.

Ford, A., and O. Bialik, "Air Pollution and Urban Factors in Relation to Cancer Mortality," Archives of Environmental Health 35(6): 335-343, November/December, 1980.

Grossarth-Maticek, R., Kanazir, D.T., Schmidt, P. and Vetter, H., "Psychosocial and Organic Variables as Predictors of Lung Cancer, Cardiac Infarct and Apoplexy -- Some Differential Predictors," Personality and Individual Differences 6(3): 313-321, 1985.

Persky, V.W., Kempthorne-Rawson, J. and Shekelle, R.B., "Personality and Risk of Cancer: 20-Year Follow-Up of the Western Electric Study," Psychosomatic Medicine 49: 435-449, 1987.

Pero, R.W., Johnson, D.B., Markowitz, M., Doyle, G., Lund-Pero, M., Seidegard, J., Halper, M. and Miller, D.G., "DNA Repair Synthesis in Individuals With and Without a Family History of Cancer," Carcinogenesis 10(4): 693-697, April, 1989.

4. Rosenblatt, M.B., "Cancer of the Lung: Diagnostic Progress in Lung Cancer: Historical Perspective," Journal of the American Geriatrics Society 16(8): 919-929, August, 1968.

Rosenblatt, M.B., "The Increase in Lung Cancer: Epidemic or Artifact?," Medical Counterpoint 1(1): 29-33, 37-39, March, 1969.

Rosenblatt, M., Statement, Re: "Cigarette Labeling and Advertising -- 1969." In: Hearings Before the Committee on Interstate and Foreign Commerce, United States, House of Representatives, Ninety-First Congress, First Session, 1255-1263, April 15-30 and May 1, 1969.

CLAIM: Smoking causes lung cancer.

RESPONSE: This is a misstatement. How can people claim that it has been proven that smoking causes lung cancer when science has not determined the mechanism by which a normal lung cell becomes cancerous?¹ Without this scientific understanding, this claim must be viewed as just that, a claim or conjecture -- not an established fact.

There is a statistical association between smoking and lung cancer, but even the first U.S. Surgeon General's Report conceded that statistical associations alone cannot prove a causal relationship.² Yet much of the existing data cited in support of a causal relationship between smoking and lung cancer is, in fact, based on statistical studies.

Moreover, eminent scientists have questioned the data on smoking and lung cancer because of its many inconsistencies and its failure to answer such basic questions as:

-- Why do the vast majority of "heavy smokers" in any study never develop lung cancer?³ On the other

hand, why do a significant percentage of nonsmokers get lung cancer?⁴

-- Why don't lung cancer rates in countries such as Japan parallel cigarette consumption? In several countries, tobacco consumption is high but the rate of lung cancer is low or vice versa.⁵

Cancer is a very complex disease. Many other factors have been associated with this disease in addition to smoking, including occupational and environmental exposures, diet, viruses, heredity, and stress.⁶ Clearly there are many gaps in knowledge about lung cancer that only further research will resolve.

REFERENCES

1. Albanes, D. and Winick, M., "Are Cell Number and Cell Proliferation Risk Factors for Cancer?," Journal of the National Cancer Institute 80(10): 772-775, July 20, 1988.
2. U.S. Department of Health, Education, and Welfare, "Criteria For Judgment," Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service, Public Health Service Publication No. 1103, Washington, D.C., U.S. Government Printing Office, Chapter 3, 17-21, 1964.
3. Herrold, K., "Survey of Histologic Types of Primary Lung Cancer in U.S. Veterans," Pathology Annual 7: 45-79, 1972.

Miller, A., "Epidemiology: Problems in the Study of Cancers of Low Incidence and the Need for Collaboration," Journal of the National Cancer Institute 54(2): 299-301, 1975.

Hehlmann, R., "Psychosomatik und Krebs (Psychosomatics and Cancer)," Münchener medizinische Wochenschrift 124(38): 829-830, September 24, 1982. Translation.

4. Enstrom, J., "Rising Lung Cancer Mortality Among Nonsmokers," Journal of the National Cancer Institute 62(4): 755-760, April, 1979.
 5. U.S. Department of Health and Human Services, Public Health Services, Office on Smoking and Health, The Health Consequences of Smoking: Cancer. A Report of the Surgeon General: 1982, DHHS Publication No. (PHS) 82-50179, 44, 1982.
- Burch, P., "The Surgeon General's 'Epidemiologic Criteria for Causality.' A Critique," Journal of Chronic Diseases 36(12): 821-836, 1983.
6. Macdonald, E., "Air Pollution, Demography, Cancer: Houston, Texas," Journal of the American Medical Women's Association 31(10): 379-395, October, 1976.

Sterling, T., "Does Smoking Kill Workers or Working Kill Smokers? Or the Mutual Relationship Between Smoking, Occupation, and Respiratory Disease," International Journal of Health Services 8(3): 437-452, 1978.

Horne, R.L. and Picard, R.S., "Psychosocial Risk Factors For Lung Cancer," Psychosomatic Medicine 41(7): 503-514, November, 1979.

Grossarth-Maticek, R., Kanazir, D.T., Schmidt, P. and Vetter, H., "Psychosocial and Organic Variables as Predictors of Lung Cancer, Cardiac Infarct and Apoplexy -- Some Differential Predictors," Personality and Individual Differences 6(3): 313-321, 1985.

Pero, R.W., Johnson, D.B., Markowitz, M., Doyle, G., Lund-Pero, M., Seidegard, J., Halper, M. and Miller, D.G., "DNA Repair Synthesis in Individuals With and Without a Family History of Cancer," Carcinogenesis 10(4): 693-697, April, 1989.

CLAIM: Lung cancer is a smoker's disease.

RESPONSE: This is simply not the case. Studies have reported finding a significant number of lung cancers among non-smokers.¹ Furthermore, not only were cases of lung cancer reported long before cigarette smoking came into popular use,² but also the vast majority of "heavy" cigarette smokers in the studies do not develop lung cancer.³

In addition, lung cancer is multi-factorial in etiology or causation. That is, many factors may be involved in the development of lung cancer. For example, in addition to smoking, occupational exposures, viruses, diet, genetic influences, food additives, pollution, stress, aging, impaired body defense mechanisms, and diesel and gas exhaust are just a few of the many risk factors that have been suggested in connection with lung cancer.⁴

Which -- if any -- of these factors plays a role in the causation of lung cancers is as of yet undetermined.

REFERENCES

1. Macdonald, E.J., Lichtenstein, H., Nooner, D., Flory, D., Wikstrom, S. and Oro, J., "Epidemiological Factors in Lung Cancer Among Women in El Paso County, Texas, 1944-1969," Journal of the American Medical Women's Association 28(9): 459-467, 1973.

Enstrom, J.E., "Rising Lung Cancer Mortality Among Nonsmokers," Journal of the National Cancer Institute 62(4): 755-760, 1979.

Schneiderman, M.A., Davis, D.L. and Wagener, D.K., "Lung Cancer That is Not Attributable to Smoking," Journal of the American Medical Association 261(18): 2635-2636, May 12, 1989.

2. Rosenblatt, M.B., "Cancer of the Lung: Facts and Fallacies," Journal of the Kentucky Medical Association 56(2): 131-136 (at 132), February, 1958.

3. Rigdon, R.H., "The Smoking Controversy," Journal of the American Medical Association 173(3): 293-295, May 21, 1960.

Herrold, K., "Survey of Histologic Types of Primary Lung Cancer in U.S. Veterans," Pathology Annual 7: 45-79, 1972.

Miller, A.B., "Epidemiology: Problems in the Study of Cancers of Low Incidence and the Need for Collaboration," Journal of the National Cancer Institute 54(2): 299-301, February, 1975.

Hehlmann, R., "Psychosomatik und Krebs (Psychosomatics and Cancer)," Münchener medizinische Wochenschrift 124(38): 829-830, September 24, 1982. Translation.

4. Macdonald, E., "Air Pollution, Demography, Cancer: Houston, Texas," Journal of the American Medical Women's Association 31(10): 379-395, October, 1976.

Sterling, T., "Does Smoking Kill Workers or Working Kill Smokers? Or the Mutual Relationship Between Smoking, Occupation, and Respiratory Disease," International Journal of Health Services 8(3): 437-452, 1978.

Horne, R.L. and Picard, R.S., "Psychosocial Risk Factors For Lung Cancer," Psychosomatic Medicine 41(7): 503-514, November, 1979.

Grossarth-Maticek, R., Kanazir, D.T., Schmidt, P. and Vetter, H., "Psychosocial and Organic Variables as Predictors of Lung Cancer, Cardiac Infarct and Apoplexy -- Some Differential

Predictors," Personality and Individual Differences 6(3): 313-321, 1985.

Fraser, D., "Lung Cancer Risk and Diesel Exhaust Exposure," Public Health Review 14(2): 139-171, 1986.

Siemiatycki, J., Dewar, R., Nadon, L., Gerin, M., Richardson, L. and Wacholder, S., "Associations Between Several Sites of Cancer and Twelve Petroleum-Derived Liquids: Results From a Case-Referent Study in Montreal," Scandinavian Journal of Work, Environment and Health, 13(6): 493-504, December, 1987.

Siemiatycki, J., Gerin, M., Stewart, P., Nadon, L., Dewar, R. and Richardson, L., "Associations Between Several Sites of Cancer and Ten Types of Exhaust and Combustion Products: Results From a Case-Referent Study in Montreal," Scandinavian Journal of Work, Environment and Health 14(2): 79-90, April, 1988.

Hayes, R.B., Thomas, T., Silverman, D.T., Vineis, P., Blot, W.J., Mason, T.J., Pickle, L.W., Correa, P., Fontham, T.H. and Schoenberg, J.B., "Lung Cancer In Motor Exhaust-Related Occupations," American Journal of Industrial Medicine 16(6): 685-695, 1989.

Pero, R.W., Johnson, D.B., Markowitz, M., Doyle, G., Lund-Pero, M., Seidegard, J., Halper, M. and Miller, D.G., "DNA Repair Synthesis in Individuals With and Without a Family History of Cancer," Carcinogenesis 10(4): 693-697, April, 1989.

CLAIM: Tests on laboratory animals have proven that cigarette smoke causes lung cancer.

RESPONSE: A review of the literature demonstrates that this statement is inaccurate. Even the 1982 U.S. Surgeon General's Report, which was the most recent to focus on cancer, conceded that attempts to induce significant numbers of lung cancer in laboratory animals have been negative.¹

People who make such statements are generally referring either to inhalation or skin painting experiments. However, as the Surgeon General's Report statement suggests, such techniques have been unsuccessful.

For example, although many inhalation experiments have been conducted, they have failed to show that inhalation of fresh, whole tobacco smoke causes human-type lung cancer in animals.² A few inhalation studies have reported the production of isolated lung cancers, but these studies have been heavily criticized for improper experimental design, the experimental procedure followed, and possible misinterpretation of the pathological findings.³

So-called skin painting experiments also have been heavily criticized for numerous reasons. These include the fact that the substances found in "tar," which is an artificially obtained laboratory product that is painted on the skins of animals in these experiments, are not found in tobacco smoke. In addition, the concentrations of "tar" used in such experiments have been extremely high. Furthermore, the skin and ears of laboratory animals are not similar to human lung tissue. Consequently, such experiments have been appropriately characterized as applying the wrong material, in the wrong form, in the wrong concentration, to the wrong tissue of the wrong animal.⁴

REFERENCES

1. U.S. Public Health Service, Office on Smoking and Health, "Mechanisms of Carcinogenesis," The Health Consequences of Smoking: Cancer. A Report of the Surgeon General: 1982, Department of Health and Human Services, Washington, D.C., U.S. Government Printing Office, DHHS Publication No. (PHS) 82-50179, Part III, 171-235 (at 218), 1982.
2. Hockett, R.C., Statement, Re: "Smoking Prevention Education Act." In: Hearings Before the Committee on Energy and Commerce, Subcommittee on Health and the Environment, United States House of Representatives, Ninety-Eighth Congress, First Session, 841-851 (at 844), March 9, 17, 1983.

Furst, A., Statement, Re: "Smoking Prevention Health and Education Act of 1983." In: Hearings before the Committee on Labor and Human Resources, United States Senate, Ninety-Eighth Congress, First Session, 465-474, May 5 and 12, 1983.
3. National Academy of Sciences, Committee on Biologic Effects of Atmospheric Pollutants, "Characteristics of Human Disease Related to Polycyclic Organic Matter." In: Biologic Effects of Atmospheric Pollutants: Particulate Polycyclic Organic Matter. Washington, D.C., National Academy of Sciences, Chapter 16, 172-190, 1972.

Feinstein, , A.R., "Clinical Biostatistics. XIX. Ambiguity and Abuse in the Twelve Different Concepts of 'Control,'" Clinical Pharmacology and Therapeutics 14(1): 112-122, 1973.

Hirth, R.S. and Hottendorf, G.H., "Lesions Produced by a New Lungworm in Beagle Dogs," Veterinary Pathology 10: 385-407, 1973.

Binns, R., "Animal Inhalation Studies With Tobacco Smoke (A Review)," Review of Environmental Health 2(8): 81-116, 1975.

Dijkstra, B.K.S., "Origin of Carcinoma of the Bronchus. Part I: The Smoking Hypothesis," South African Cancer Bulletin 21(1): 7-16, January/March, 1977.
4. Hockett, R., "Where Do We Go From Here in Tobacco and Health Research?," Presentation Before the Burley and Dark Leaf Tobacco Export Association, Lexington, Kentucky, October 2, 1967.

Hockett, R.C., Statement, Re: "Public Health Cigarette Amendments of 1971." In: Hearings Before the Committee on Commerce, Consumer Subcommittee, United States Senate, Ninety-

Second Congress, Second Session, 97-123, February 1, 3, and
10, 1972.

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CIGARETTE INGREDIENTS

CAVEAT: The information contained in this paper regarding the use of non-tobacco ingredients in cigarettes is based primarily on information obtained from, and the experience of, cigarette manufacturers in the United States. To the extent that statements regarding the use of non-tobacco ingredients in cigarettes and other tobacco products may be made based on information contained in this paper, be advised that the number, quantity, and type of non-tobacco ingredients added to cigarettes in other parts of the world, and the specific identity of such non-tobacco ingredients, may not correspond to the use and experience of American manufacturers as described in this paper.

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INTRODUCTION

Non-tobacco ingredients are used in the manufacture of cigarettes and other tobacco products for a variety of reasons. For example, these ingredients improve the balance of smoke in terms of taste, flavor, or burning characteristics. Such substances have been added to tobacco since the American Indians introduced smoking to European explorers. In addition, many ingredients added to tobacco also occur naturally in tobacco, such as sugar.

The extent to which non-tobacco ingredients are used to improve properties of tobacco products has varied considerably from country to country and time to time. For example, the "All Virginia" cigarettes of the United Kingdom and the traditional dark, air-cured cigarettes of France made minimal use of non-tobacco ingredients. In contrast, "American-style" cigarettes have generally utilized a wide variety of such substances. Today, however, non-tobacco ingredients are used in the manufacture of virtually all tobacco products throughout the world, including "Virginia" cigarettes.

Non-tobacco ingredients generally fall into four categories -- flavorings, casing materials, humectants, and processing aids. The majority of the ingredients utilized are flavorings which are used to enhance the taste and refine the smoking qualities of cigarettes. As such, flavorings are an

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integral part of tobacco products. They contribute to the overall impression of the product through their effect on the taste of smoke and the smell of the cigarettes. Flavorings make the major contribution to the distinctive taste and aroma of the many individual brands and styles of cigarettes.

Flavorings are generally natural components, such as menthol, spices, and citrus, or synthetics that have been developed to provide the flavor and aroma characteristic of natural materials. Menthol is probably the best known ingredient added to tobacco in cigarettes as a flavoring.

In addition to flavorings, cigarettes also contain casing materials. The precise ingredients used to achieve these desired results depend upon the style of the tobacco product involved in terms of both the tobacco used and delivery constraints which must be achieved. For example, traditional "Virginia" cigarettes contain natural sugars while light air-cured tobaccos (which comprise a significant part of blended cigarettes) have negligible levels. Treatment of these air-cured tobaccos with quantities of sugars and other materials in the form of a "casing" is necessary to develop their character and make for smoother smoke.

Humectants and moisturizers, such as glycerol or propylene glycol, are also used in the manufacture of cigarettes

throughout the world. Humectants help to stabilize the tobacco moisture content and smoking properties that may result from fluctuations in temperature and humidity. The need for these ingredients varies both with product type and the circumstances in which the product is marketed.

Finally, processing aids, such as carbon dioxide, are used for a variety of purposes, including the adjustment of nicotine levels in tobacco, which varies from crop to crop, and the expansion or "puffing" tobacco in the production of lower "tar" and nicotine brands. Processing aids are present in finished cigarettes in trace quantities, if at all.

SUBSTANCES USED IN TOBACCO
MANUFACTURING ARE ALSO USED IN OTHER PRODUCTS

Most of the ingredients used in cigarettes have a long history of use in foods, confections, and beverages and have been reviewed for use in these products by a variety of governmental agencies. For example, most non-tobacco ingredients used in cigarettes manufactured in the United States are included in the lists of substances "Generally Recognized as Safe" (GRAS) as determined by the U.S. Food & Drug Administration (FDA) and by the U.S. Flavor and Extract Manufacturers Association (FEMA).

AMOUNTS OF NON-TOBACCO INGREDIENTS ADDED TO CIGARETTES

The amount of ingredients incorporated into tobacco products vary by weight from a few percent, e.g., casings (such as sugars, cocoa, licorice extract, etc.) and humectants (glycerol, propylene glycol, etc.) used traditionally in blended cigarettes, down to even smaller amounts of flavorings. Flavor substances similar to those used in the manufacture of food and drink, or identical to those found in tobacco itself, are used as "top flavors" in very small amounts. "Top flavors" help give cigarette brands their distinctive taste and aroma and, in the aggregate, normally constitute less than one tenth of one percent by weight of the final product.

A small number of casing materials, moisturizers and major flavorings account for the great bulk of ingredients actually in a cigarette. Approximately 25 substances (casings, humectants, and processing aids) comprise over 99% of the total amount, by weight, of non-tobacco ingredients used in the manufacture of cigarettes in the United States. As noted, any ingredients used as processing aids (e.g., carbon dioxide) in a finished cigarette are present only in trace quantities, if at all.

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REGULATION OF CIGARETTE INGREDIENTS

The identities of specific ingredients used in cigarettes and the mixture of ingredients comprising the recipe for any individual brand are closely-guarded trade secrets of the manufacturer. These ingredients make major contributions to the taste and appeal of individual brands. Disclosure of the ingredients used in cigarette manufacture could reveal product formulas that have required years of research to develop and cause irreparable damage to the manufacturer in a highly competitive industry. Although a wide range of ingredients used in tobacco products have been listed with governmental agencies and mentioned in other publications, specific recipes are closely-guarded trade secrets.

The issue of the addition of non-tobacco ingredients to tobacco products developed in part as a parallel response to regulatory activities in other areas such as food additives. Historically, regulation of tobacco ingredients has been a response to interest expressed in some countries over possible adulteration of consumer products in general.

Governmental bodies in several countries, including Great Britain, Canada, and Germany, have reviewed and approved, a large

number of non-tobacco ingredients for use in cigarettes. For example, in 1973 the Independent Scientific Committee on Smoking and Health ("ISCSH") was set up in the Great Britain in order to advise the British government on scientific aspects of matters concerning smoking and health, and, in particular, to compile lists (known as the "ISCSH" lists) of allowed and prohibited additives to tobacco products. Non-tobacco ingredients approved for use in tobacco products were those "a) for which after long-term usage no evidence has emerged of their harmful effect (long-term being defined as in constant use for 20 years or more); or b) for which the results of toxicity testing by a manufacturer have been reported to, and have satisfied, the Committee."¹ The ISCSH was charged with specifically prohibiting the use of non-tobacco ingredients which on pyrolysis (or burning) might, in the ISCSH's view, produce a potential or known health risk or for which the results of toxicity testing have not satisfied the ISCSH.

Any company proposing to market a cigarette in Great Britain containing non-tobacco ingredients must abide by the ISCSH guidelines in all respects. The ISCSH periodically reviews and updates its lists and considers its system to "work well."² According to the fourth and most recent report of the ISCSH, "The Committee will continue to ensure the safety of additives used in all smoked tobacco products."³

Other governmental bodies also maintain lists of substances that may not be added to cigarettes. For example, German ordinances specifically prohibit the use of certain substances as ingredients in tobacco products which, in general, were determined to be harmful as food additives. Manufacture or import of cigarettes containing such ingredients is prohibited in Germany.

Since 1986, the six major cigarette manufacturers in the United States have annually provided the U.S. Department of Health and Human Services (DHHS) with lists of non-tobacco ingredients added to tobacco in the manufacture of cigarettes in the United States. These lists have been submitted pursuant to the requirements of the 1984 Federal Cigarette Labeling and Advertising Act. The DHHS is required to review the lists and prepare a report to the U.S. Congress on the health effects, if any, associated with the use of those ingredients. To date, five yearly lists have been submitted, although no report has been issued from the DHHS.⁴ Non-tobacco ingredients used in cigarette filters and paper are not included in the United States submissions. The German and Great Britain (ISCSH) lists, however, also regulate the use of non-tobacco ingredients in cigarette filters and paper.

Legislation regulating non-tobacco ingredients has been slow to develop outside Europe. The absence of such legislation may well reflect the lack of any convincing evidence that the use

of non-tobacco ingredients in cigarettes and other tobacco products has any deleterious effects on consumers.

CLAIMS CONCERNING HEALTH RISKS

Cigarette manufacturers and various government agencies have tested the major use ingredients through various bioassays such as the "Ames" test and, in some cases, have conducted animal studies of individual ingredients and combinations of ingredients. These tests typically involve two, five, or even 10 times or more than the amount of the ingredient used in a commercial cigarette. None of these studies indicate that the use of ingredients in cigarettes cause disease in smokers. Moreover, none of the substances currently used by the six major United States cigarette manufacturers are considered potential carcinogens by the National Toxicology Program (NTP), the International Agency for Research on Cancer (IARC) or any other recognized organization which evaluates the toxicity of substances.

Furthermore, 19 of the 25 ingredients that comprise over 99% of the total amount, by weight, of the non-tobacco substances added to tobacco in cigarettes manufactured or sold in the U.S. are listed as "Generally Recognized as Safe" (GRAS) or otherwise approved for use as food additives by FEMA or the FDA. Twenty are approved by Great Britain's ISCSH for use in cigarettes at

prescribed levels. None are prohibited for use in cigarettes by any government ordinance.

LEGISLATIVE CONSIDERATIONS

Legislation regarding the use of ingredients in tobacco products creates a number of potential consequences which must be considered. Under some circumstances, such regulation could lead to restrictions on trade where it is particularly disadvantageous to one or another product type. Moreover, as noted earlier, disclosure of non-tobacco ingredients themselves presents a difficult issue, particularly with regard to recipes which may consist of complex, proprietary formulations developed and maintained as trade secrets by manufacturers in the tobacco industry, as well as the food and beverage industry. For example, the ingredient lists submitted to the DHHS are subject to strict confidentiality requirements which prevent their release or disclosure to the public or media and restrict the distribution of the list within the Department.⁵

Tobacco manufacturers and their suppliers fully understand the need to carefully monitor the materials used in their products and, in fact, maintain continuing review. There is no compelling evidence that indicates that the imposition of legislation or regulation in this area has any additional consumer benefit.

REFERENCES

1. Department of Health and Social Security, Northern Ireland Office, Scottish Home and Health Department, Welsh Office, First Report of the Independent Scientific Committee on Smoking and Health: Tobacco Substitutes and Additives in Tobacco Products, London, Her Majesty's Stationery Office, 1-29 (at 28), 1975.
2. Department of Health and Social Security, Department of Health and Social Services, Northern Ireland, Scottish Home and Health Department, Welsh Office, Fourth Report of the Independent Scientific Committee on Smoking & Health, London, Her Majesty's Stationery Office, 1-68 (at 26), 1988.
3. Department of Health and Social Security, Department of Health and Social Services, Northern Ireland, Scottish Home and Health Department, Welsh Office, Fourth Report of the Independent Scientific Committee on Smoking & Health, London, Her Majesty's Stationery Office, 1-68 (at 26), 1988.
4. Whitley, C.O., Statement, Re: "Tobacco Control and Health Protection Act." During: Hearings Before the Committee on Energy and Commerce, Subcommittee on Health and the Environment, 1-44, July 12, 1990.
5. Federal Cigarette Labeling and Advertising Act, Pub. L. No. 98--474, 98 Stat. 2204 (1984).

INGREDIENTS

CLAIMS/RESPONSES

CLAIM: Cigarette manufacturers add harmful substances to tobacco when they make cigarettes that they don't want to tell the public about.

RESPONSE: In some countries, substances generally called "ingredients" are added to tobacco, for example, to improve its flavor, taste, or burning characteristics. Consequently, these substances make major contributions to the distinct flavor and aroma of individual brands and types of cigarettes.

Most of these substances have a long history of use in foods, confections, and beverages and have been reviewed for use in these products by a variety of governmental agencies such as the Food and Drug Administration in the United States.

Since these ingredients make major contributions to the taste and appeal of individual brands, manufacturers are naturally concerned about revealing the identities of specific ingredients used in cigarettes and the mixture of ingredients comprising the recipe for any individual brand. Such disclosure could reveal product formulas that have required years of research to develop and could

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cause irreparable damage to the manufacturer in a highly competitive industry. Although a wide range of ingredients used in tobacco products have been listed with governmental agencies and mentioned in other publications, specific recipes have the highest commercial value and are closely guarded trade secrets.

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CLAIM: Cigarette ingredients should be regulated.

RESPONSE: Governmental bodies in several countries, including Great Britain and Germany, already review and approve a large number of non-tobacco ingredients for use in cigarettes. In Great Britain, for example, the Independent Scientific Committee on Smoking and Health ("ISCSH") was set up in order to advise the British government on scientific aspects of matters concerning smoking and health and, in particular, to compile lists of allowable and prohibited ingredients to tobacco products. Non-tobacco ingredients approved for use by the ISCSH must meet certain criteria regarding safety and health.

Other governmental bodies also maintain lists of substances that may not be added to cigarettes. For example, German ordinances specifically prohibit the use of certain substances as ingredients in tobacco products where, in general, these substances were determined to be harmful as food additives. Manufacture or import of cigarettes containing listed ingredients is prohibited in that country. In the United States, the six major cigarette manufacturers have been required since 1986 to provide the United States Department of Health and Human Services (DHHS) with annual lists of non-tobacco

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ingredients added to tobacco in the manufacture of cigarettes in that country. The DHHS is required to review the lists and submit a report to the U.S. Congress on the health effects, if any, associated with the use of those ingredients. To date, lists for five years have been submitted, but no report has been issued by the DHHS.

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CLAIM: Non-tobacco ingredients in cigarettes are harmful to the smoker.

RESPONSE: Many of the ingredients that comprise the large bulk of non-tobacco ingredients added to tobacco in cigarettes in, for example, the United States, Great Britain, and Germany are either on lists approved for use as food additives or are approved or disapproved for use by specific government ordinances. Cigarette manufacturers and various government agencies have tested those ingredients used most often through various bioassays and, in some cases, have conducted animal studies of individual ingredients and combinations of ingredients. These studies typically involve two, five, or even 10 times or more the amount of the ingredient used in a commercial cigarette. Such studies have not shown that the use of ingredients in cigarettes causes disease in smokers.

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**TOBACCO SMOKE CONSTITUENTS:
EXECUTIVE SUMMARY**

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I

Tobacco smoke has been the subject of intensive research over many years, in an effort to identify the constituents of smoke and to determine what effect, if any, smoking may have on humans. By some estimates, over 4,000 constituents of cigarette smoke have been identified thus far, and such research is continuing. No constituent as found in cigarette smoke, however, has been scientifically proven to cause cancer or any other human disease.¹

II

Ninety percent of cigarette smoke is air, water and carbon dioxide, a natural by-product of combustion. Of the remaining 10 percent, only a few substances such as nicotine and carbon monoxide (CO) are detectable at levels above one milligram per cigarette. The vast majority of the remaining compounds in cigarette smoke are present only in extremely small amounts, measured in micrograms (millionths of a gram) or nanograms (billionths of a gram) per cigarette. Although under experimental conditions, involving laboratory animals, some substances in cigarette smoke may have a toxic or disease-inducing effect, the concentrations at which a smoker is exposed to these same substances have not been demonstrated to cause disease in humans.

III

"Tar" is frequently the subject of public comment and criticism by anti-smoking advocates as causing cancer in smokers. "Tar" is an artificially created laboratory product consisting of highly concentrated and physically altered cigarette smoke particulate matter which is collected either by passing cigarette smoke through a cold trap at extremely low temperatures or by using filters and a drying process. That may be why this product is sometimes referred to as condensate. No human smoker is exposed to "tar" in the form that it is used for experimentation in the laboratory.

Nevertheless, such "tar" has been the subject of animal experiments to investigate the possible relationship between tobacco smoke and cancer. In those experiments, "tar" was repeatedly painted on the shaved backs or ears of test animals over prolonged periods of time. Some of these tests resulted in the production of tumors. These test results, however, should not and cannot be extrapolated to the human smoker. The differences in the method of exposure between skin painting experiments and smoking are obvious. Likewise the concentrations of "tar" used in such experiments are extremely high. Consequently, such experiments have been said to involve applying "the wrong material in the wrong form, in the wrong dosage, to the wrong tissue of the wrong animal."²

IV

Nicotine is present in cigarette smoke because it is a natural element of tobacco. Anti-smoking advocates often blame nicotine for the development of heart disease. Yet no biological mechanism by which nicotine, or any other agent, may be involved in heart disease has been demonstrated. Moreover, no correlation between the nicotine level of the cigarette or the number of cigarettes smoked and the smoker's actual nicotine intake has been established because of individual variations of puff rates, depth of inhalation, and body metabolism.³

V

CO is produced by burning cigarettes, as it is also produced by many natural and man-made sources, including automobile exhaust and industrial emissions. In comparison to most other sources, the exposure to CO from smoking has been described as "insignificant."⁴ Still, anti-smoking advocates often assert that CO plays a role in the causation of cardiovascular disease. However, the question of whether exposure to CO from cigarette smoke causes disease in smokers remains unanswered.⁵

VI

Increased attention has been focused on the presence of other constituents in cigarette smoke, some of which may have a toxic effect on or be associated with disease in animals or humans

at levels and under conditions of exposure greatly different than those encountered by the smoker. Such substances as acetone, ammonia, arsenic, methanol, nitrosamines and phenol -- present in cigarette smoke -- are present everywhere in the environment. They are produced whenever organic matter is burned, whether in industrial emissions, through smoking, or in grilling a steak. The level of exposure to these substances from cigarette smoking is extraordinarily low, and the suggestion that there is something "unique" about the smoker's exposure to these substances is scientifically misleading.

VII

Acetaldehyde is reportedly present in minute quantities in cigarette smoke. Although it is an eye and skin irritant (and sometimes toxic) at high levels of exposure, the available data are considered "inadequate" to establish that exposure to acetaldehyde at any level causes cancer in humans.⁶

VIII

Acetone has been reported to be present in minute quantities in the vapor phase of cigarette smoke. It has been detected in freeze dried foods and dried milk, and is a naturally occurring constituent of human blood and human. Acetone is not considered toxic at low levels of exposure.⁷

IX

Acrolein has been reported to be present in small quantities in the vapor phase of cigarette smoke. It is present everywhere in the environment as a product of fires, automobile exhaust, and other industrial emissions. Acrolein is also produced by burning foods containing fat, such as grilling a steak. It has been stated that "there is no evidence" to support the claim that acrolein is a human carcinogen.⁸

X

Ammonia is reportedly detectable in minute amounts in cigarette smoke. It occurs naturally as a part of protein metabolism in man and virtually all species of animals. Although ammonia at high concentrations is an irritant, the amount of ammonia in cigarette smoke is so low that one researcher has concluded that its significance to the human smoker is "purely conjectural."⁹

XI

Arsenic is a natural occurring metal that is drawn into growing tobacco (and other plants) from the soil. It is also present in rocks, water, and virtually all living organisms. Although arsenic has sometimes been indicated as a possible carcinogen in animal experiments, its relationship to disease in smokers is considered "speculative."¹⁰

XII

Benzene has been reported to be present in small quantities in the vapor phase of cigarette smoke. Although benzene has sometimes been suggested as a possible cause of leukemia, leukemia has not been consistently linked to cigarette smoking in the various statistical studies that form the primary basis for public health criticism of smoking.¹¹

XIII

Benzo(a)pyrene (BaP) is sometimes singled out as a human carcinogen because it is a component of the laboratory product "tar," which has been reported to produce tumors under the highly artificial conditions involved in animal skin painting experiments. BaP is formed by the incomplete combustion of organic matter. In addition to cigarette smoke, other sources of BaP in the atmosphere are coal and oil fired power stations, domestic heating, automobile exhaust, industrial emissions, forest fires and volcanic activity. BaP is detectable in fish, meat and vegetables, as well as in drinking water.¹²

XIV

Butane may be present in the vapor phase of cigarette smoke in minute quantities. It occurs in natural gas and is present in the atmosphere as the result of the combustion of gasoline and

other petroleum products. The inhalation of butane has not been reported to have chronic health effects in humans.¹³

XV

Cadmium is a trace "heavy metal" present in tobacco and in cigarette smoke. The principal sources of cadmium exposure for man are from food, dairy products and drinking water. It has been observed that the data for the claimed carcinogenicity of cadmium in cigarette smoke in humans is "very limited."¹⁴

XVI

Chromium is drawn into growing tobacco from the soil. As chromium is a naturally-occurring constituent of the earth's crust, it is present virtually everywhere in the environment, in the soil, in water, and in the atmosphere. The most significant sources of chromium intake for most people are through food and water. Although some studies of chromate-industry workers have caused concern about a possible role of chromium exposure in human disease, the level of chromium to which a smoker may be exposed is vastly lower.¹⁵ In fact, some researchers have concluded that none of the chromium in cigarette tobacco is transferred into mainstream smoke.¹⁶

XVII

Hydrogen cyanide (HCN) is reportedly present in minute amounts in the vapor phase of cigarette smoke. HCN is also generated by the combustion of carbon materials in air, for example, during home cooking. It is also present in such varied food products as bitter almonds, lima beans, soybeans, apricots and linseed. The level of HCN in cigarette smoke is extremely low, and research indicates that it is rapidly eliminated from the smoker's system.¹⁷

XVIII

Lead is drawn from the soil into growing tobacco. It is present in the air, soil and water, and all persons are exposed to and ingest small amounts of lead each day. The incremental additional exposure of a smoker to lead is considered to be inconsequential compared to the intake of lead from other sources.¹⁸

XIX

Methanol is reported to be present in very small quantities in cigarette smoke as a vapor phase component. It is also present in bread, soy sauce and various fruits and vegetables. Although in large concentrations methanol can be a skin and eye irritant, one researcher stated he was unable to find any studies showing the inhalation of methanol in the amounts present in cigarette smoke to be carcinogenic.¹⁹

XX

Naphthalene is reportedly present in small quantities both in "tar" and in the vapor phase of cigarette smoke. It is created by the combustion of tobacco and other organic materials. In the home, it is found frequently in air fresheners, moth balls, varnishes and wood preservatives. Naphthalene has no conclusive reported carcinogenic effect, although is sometimes associated with leukemia in animal experiments. Leukemia has not been consistently statistically associated with cigarette smoking in the scientific literature.²⁰

XXI

Nickel is drawn from the soil into growing tobacco. The amount of nickel reportedly to be present in tobacco and transferred into cigarette smoke is very small. Researchers have agreed that there is no credible scientific data that nickel as found in cigarette smoke has been shown to cause disease in smokers.²¹

XXII

Cigarette smoke is said to contain nitric oxide, but very little, if any, nitrous oxide or nitrogen oxide.²² It has been noted that both smokers and non-smokers maintain consistently low levels of nitric oxide in their blood.²³

XXIII

Nitrosamines reportedly are detectable in both "tar" and in the vapor phase component of cigarette smoke. Nitrosamines are also found in soil, air, water and food. Under experimental conditions, certain nitrosamine compounds have been noted to produce tumors in laboratory animals. However, even the U.S. Surgeon General has stated that there is "a lack of direct evidence" that the nitrosamines specific to tobacco cause cancer in smokers.²⁴

XXIV

Phenol is reported to be present in minute quantities in cigarette smoke. It occurs naturally in animal tissues; the consumption of meat has been identified as a primary source of human exposure to phenol. Researchers have stated that phenol is not present in cigarette smoke at high enough concentrations to cause disease in smokers.²⁵

XXV

Polonium-210 is a radioactive element that has been reported to be present in trace amounts in tobacco and cigarette smoke. It is also present in the atmosphere and in soil. Researchers have discounted the claimed risk to smokers, noting the extraordinarily minute quantities at which it is present in cigarette smoke.²⁶

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XXVI

Toluene is reported to be a constituent of the vapor phase component of cigarette smoke. It is also present in the atmosphere as a result of industrial emissions, automobile exhaust and gasoline evaporation. Although it is an eye and skin irritant at low levels and concentrations, toluene has not been reported to be toxic or to cause chronic disease in humans at those levels.²⁷

XXVII

Urethane is reportedly present in cigarette smoke in very small amounts. It is also a natural by-product of fermentation, and is found in wines, distilled spirits, and beer, as well as in fermented food products such as cheese, yogurt and soy sauce. Although urethane has been suggested as a possible animal carcinogen, even the U.S. Surgeon General has stated it is not present in cigarette smoke in sufficient quantities to cause cancer in smokers.²⁸

XXVIII

Vinyl chloride has been reported to be present in minute amounts in the vapor phase of cigarette smoke. It is also present in various food products such as honey, butter and ketchup and in some wines. It has been stated that vinyl chloride is present in cigarette smoke at levels too low to be considered carcinogenic.²⁹

REFERENCES

1. Okun, R., Statement, Re: "Cigarette Smoking and Disease, 1976." In: Hearings Before the Committee on Labor and Public Welfare, Subcommittee on Health, United States Senate, Ninety-Fourth Congress, Second Session, 152-167, February 19, March 24, and May 27, 1976.
2. Hockett, R.C., Statement, Re: "Public Health Cigarette Amendments of 1971." In: Hearings Before the Committee on Commerce, Consumer Subcommittee, United States Senate, Ninety-Second Congress, Second Session, 97-122 (at 102), February 1, 3, and 10, 1972.

Hockett, R.C., Statement, Re: "Comprehensive Smoking Prevention Education Act." In: Appendix to Hearings Before the Committee on Energy and Commerce, Subcommittee on Health and the Environment, United States House of Representatives, Ninety-Seventh Congress, Second Session, 627-635 (at 635), March 5, 11 and 12, 1982.
3. Langone, J.J., Gjika, H.B. and Van Vunakis, H., "Nicotine and Its Metabolites. Radioimmunoassays for Nicotine and Cotinine," Biochemistry 12(24): 5025-5030, 1973.
4. Wakeham, H.R.R., "Environmental Carbon Monoxide from Cigarette Smoking -- A Critique," Preventive Medicine 6: 526-534 (at 526), 1977.
5. Weir, F.W. and Fabiano, V.L., "Re-Evaluation of the Role of Carbon Monoxide in Production or Aggravation of Cardiovascular Disease Processes," Journal of Occupational Medicine 24(7): 519-525, July, 1982.
6. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, "Acetaldehyde (Group 2B)," IARC Monographs On the Evaluation of Carcinogenic Risks to Humans. Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42. Supplement 7, 77-78 (at 77), 1987.
7. Krasavage, W.J., O'Donoghue, J.L., and DiVincenzo, G.D., "Ketones." In: Chapter Fifty-Six. Patty's Industrial Hygiene and Toxicology. Third Revised Edition. G.D. Clayton and F. E. Clayton (eds.). New York, John Wiley & Sons, 4709-4800 (see particularly 4724-4726), 1982.

8. Beauchamp, R.O., Andjelkovich, D.A., Kligerman, A.D., Morgan, K.T. and Heck, H.d'A., "A Critical Review of the Literature on Acrolein Toxicity," CRC Critical Reviews in Toxicology 14(4): 309-380 (at 342), 1985.
9. Huber, G.L., "Physical, Chemical, and Biologic Properties of Tobacco, Cigarette Smoke, and Other Tobacco Products," Seminars in Respiratory Medicine 10(4): 297-332 (at 316), October, 1989.
10. Huber, G.L., "Physical, Chemical, and Biologic Properties of Tobacco, Cigarette Smoke, and Other Tobacco Products," Seminars in Respiratory Medicine 10(4): 297-332 (at 313), October, 1989.
11. Huber, G.L., "Physical, Chemical, and Biologic Properties of Tobacco, Cigarette Smoke, and Other Tobacco Products," Seminars in Respiratory Medicine 10(4): 297-332 (see particularly 312, 316), October, 1989.
12. Osborne, M.R. and Crosby, N.T., "Occurrence of Benzopyrenes in the Environment." In: Benzopyrenes. M.M. Coombs, J. Ashby, R.F. Newbold and H. Baxter (eds.). Cambridge, Cambridge University Press, Chapter 17, 301-316, 1987.

Sandmeyer, E.E., "Chapter Forty-Seven. Aromatic Hydrocarbons. 4. Tri- and Polynuclear Ring Systems." In: Patty's Industrial Hygiene and Toxicology. Third Revised Edition. G.D. Clayton and F.E. Clayton (eds.). New York, John Wiley & Sons, 3253-3431 (see particularly 3345), 1982.
13. Sandmeyer, E.E., "Chapter Forty-Five. Aliphatic Hydrocarbons. 1.5. Butanes." In: Patty's Industrial Hygiene and Toxicology. Third Revised Edition. G.D. Clayton and F.E. Clayton (eds.). New York, John Wiley & Sons, 3182-3183, 1982.

Beall, J.R. and Ulsamer, A.G., "Toxicity of Volatile Organic Compounds Present Indoors," Bulletin of The New York Academy of Medicine 57(10): 978-997 (see particularly 980), December, 1981.
14. Huber, G.L., "Physical, Chemical, and Biologic Properties of Tobacco, Cigarette Smoke, and Other Tobacco Products," Seminars in Respiratory Medicine 10(4): 297-332 (at 313), October, 1989.
15. Huber, G.L., "Physical, Chemical, and Biologic Properties of Tobacco, Cigarette Smoke, and Other Tobacco Products," Seminars in Respiratory Medicine 10(4): 297-332 (see particularly 313), October, 1989.

16. Fan, A.M. and Harding-Borlow, I., "Chromium." In: Advances in Modern Environmental Toxicology. Volume XI. Genotoxic and Carcinogenic Metals: Environmental and Occupational Occurrence and Exposure, L. Fishbein, A. Furst and M.A. Mehlman (eds.). Princeton, Princeton Scientific Publishing Co., Inc., 87-125 (see particularly 89), 1987.
17. Lundquist, P., Rosling, H., Sörbo, B. and Tibbling, L, "Cyanide Concentrations in Blood After Cigarette Smoking, as Determined by a Sensitive Fluorimetric Method," Clinical Chemistry 33(7): 1228-1230, 1987.
18. WHO International Agency for Research on Cancer, The Evaluation of the Carcinogenic Risk of Chemicals to Humans, Lyon, World Health Organization, IARC Monograph No. 23, 325-416, 1971.
19. Marnett, L.J., "Health Effects of Aldehydes and Alcohols in Mobile Source Emissions." In: Air Pollution, The Automobile and Public Health. Washington, D.C., National Academy Press, 579-603 (see particularly 587), 1988.
20. Huber, G.L., "Physical, Chemical, and Biologic Properties of Tobacco, Cigarette Smoke, and Other Tobacco Products," Seminars in Respiratory Medicine 10(4): 297-332 (see particularly 312), October, 1989.
21. Huber, G.L., "Physical, Chemical, and Biologic Properties of Tobacco, Cigarette Smoke, and Other Tobacco Products," Seminars in Respiratory Medicine 10(4): 297-332 (see particularly 313), October, 1989.
- Wynder, E.L. and Hoffmann, D., Tobacco and Tobacco Smoke: Studies in Experimental Carcinogenesis, New York, Academic Press Inc., 493, 498, 627-628, 1967.
22. Huber, G.L., "Physical, Chemical, and Biologic Properties of Tobacco, Cigarette Smoke, and Other Tobacco Products," Seminars in Respiratory Medicine 10(4): 297-332 (at 315), 1989.22.
23. U.S. Department of Health, Education, and Welfare, Public Health Service, Office on Smoking and Health, "14. Constituents of Tobacco Smoke: Toxicity of Specific Smoke Components," Smoking and Health. A Report of the Surgeon General, DHEW Publication No. (PHS) 79-50066, Washington, D.C., U.S. Government Printing Office, 78-84 (see particularly 80), 1979.
24. U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health, "Part III. Mechanisms of Carcinogenesis: Experimental Carcinogenesis With Tobacco Smoke," The Health Consequences of Smoking: Cancer. A Report

10269254

of the Surgeon General: 1982, DHHS Publication No. (PHS) 82-50179, Washington, D.C., U.S. Government Printing Office, 181-235 (at 200), 1982.

25. Kensler, C.J., Battista, S.P. and Thayer, P.S., "19. Animal Models for the Study of Tobacco Carcinogenesis." In: Human Epidemiology and Animal Laboratory Correlations in Chemical Carcinogenesis. Frederick Coulston and Philippe Shubik (eds.). Norwood, New Jersey, Ablex Publishing Corporation, 341-357 (see particularly 351), 1980.
26. Cohen, B.S., Eisenbud, M. and Harley, N.H., "Measurement of the Alpha-Radioactivity on the Mucosal Surface of the Human Bronchial Tree," Health Physics 39(4): 619-632, 1980.

Harley, N.H., Cohen, B.S. and Tso, T.C., "Polonium-210: A Questionable Risk Factor in Smoking-Related Carcinogenesis." In: Banbury Report 3: A Safe Cigarette? G. B. Gori and F. G. Bock (eds.). Cold Spring Harbor, New York, Cold Spring Harbor Laboratory, 93-104, 1980.
27. Gibson, J.E. and Hardisty, J.F., "Chronic Toxicity and Oncogenicity Bioassay of Inhaled Toluene In Fischer-344 Rats," Fundamental and Applied Toxicology 3: 315-319, July/August, 1983.

Häsänen, E., Karlsson, V., Leppämäki, E. and Juhala, M., "Short Communication: Benzene, Toluene and Xylene Concentrations in Car Exhausts and in City Air," Atmospheric Environment 15(9): 1755-1757, 1981.

Carpenter, C.P., Geary, D.L. Jr., Myers, R.C., Nachreiner, D.J., Sullivan, L.J. and King, J.M., "Petroleum Hydrocarbon Toxicity Studies. XIII. Animal and Human Response to Vapors of Toluene Concentrate," Toxicology and Applied Pharmacology 36(3): 473-490, 1976.
28. U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health, "Part III. Mechanisms of Carcinogenesis: Experimental Carcinogenesis With Tobacco Smoke," The Health Consequences of Smoking: Cancer. A Report of the Surgeon General: 1982, DHHS Publication No. (PHS) 82-50179, Washington, D.C., U.S. Government Printing Office, 181-235 (see particularly 194), 1982.
29. Huber, G.L., "Physical, Chemical, and Biologic Properties of Tobacco, Cigarette Smoke, and Other Tobacco Products," Seminars in Respiratory Medicine 10(4): 297-332 (at 316), October, 1989.

TOBACCO SMOKE CONSTITUENTS

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I. INTRODUCTION

Tobacco smoke is a highly complex mixture containing, by some estimates, over 4,000 constituents. Over the years, much time and effort has been devoted to determining the identity of tobacco smoke constituents. This has proven difficult, however, and much remains to be learned about the structure and makeup of tobacco smoke and its relationship, if any, to human disease.

Ninety percent of cigarette smoke is air, water and carbon dioxide, a natural by-product of combustion. Of the remaining 10 percent, only a few substances such as nicotine and carbon monoxide (CO) have been measured by researchers as being present in smoke at levels above one milligram per cigarette. Anti-smoking advocates frequently assert that nicotine and CO cause disease in humans. The same is also said about "tar," even though it is a laboratory product, not an actual constituent of tobacco smoke.

The vast majority of the remaining constituents actually present in cigarette smoke, some of which have been identified in "tar," are present only in extremely small amounts, measured in micrograms (millionths of a gram) or nanograms (billionths of a gram) per cigarette. Nonetheless, anti-smoking advocates occasionally single out for public criticism certain smoke constituents other than "tar," nicotine and CO that have, under conditions and at levels vastly different from those to which a human smoker is

exposed, been associated with disease in animals or humans. These substances, however, are ubiquitous. Smokers and non-smokers alike are exposed to most of these substances every day simply by breathing air, drinking water and eating food.

The significance of smoke constituents to human health, if any, is not yet understood. According to one researcher in the area, "no ingredient [constituent] or group of ingredients [constituents] as found in tobacco smoke have been established as disease producing in smokers."¹

II. SMOKE CONSTITUENTS

A. "Tar"

"Tar" is an artificially created laboratory product consisting of highly concentrated and physically altered cigarette smoke particulate matter which is gathered either by passing cigarette smoke through a cold trap at extremely low temperatures or by using filters and a drying process. The substances as found in "tar" are not found in cigarette smoke. That may be why this product is sometimes referred to as condensate. Certainly, material collected in this way does not duplicate what humans are exposed to when they smoke. As a report on a meeting of experts in the area noted:

[T]here is, at present, no available instrumentation permitting the separation and

individual collection of the particulate and gas phases which duplicates the precise physico-chemical conditions prevailing in cigarette smoke as it is inhaled.²

Despite its apparent lack of relevance to smoking, laboratory-produced "tar" has been used in animal experiments designed to investigate the possible relationship between tobacco smoke and cancer. In those experiments, "tar" was repeatedly painted on the shaved backs or ears of test animals over prolonged periods of time. These so-called skin-painting experiments have prompted a great deal of interest, as the tumors which resulted have been said to be evidence that tumors might develop in human lungs from inhaling cigarette smoke.

The results of such animal experiments cannot and should not be extrapolated to the human situation. Even if the "tar" collected by the methods described above were present in cigarette smoke, the "tar" used in skin painting experiments is very different by the time it is studied in the laboratory. That is because after "tar" is collected, it continues to undergo chemical changes as long as it is stored.³ Furthermore, as an experimental toxicologist has noted, even if an effect such as tumor production is observed in a particular species, that does not necessarily mean that it might "occur either quantitatively or qualitatively in man."⁴

Skin painting experiments suffer from a number of additional weaknesses. For example, the concentrations of "tar" used in such experiments are extremely high. It has been estimated that the amounts utilized would be equivalent to an individual smoking over 100,000 cigarettes per day.⁵ Furthermore, the skin and ears of laboratory animals are not similar to human lung tissue. Animal skin lacks the intricate clearance mechanisms of the lungs, such as the mucus blanket which coats the lining of the major airways of the lung. Even the summary report of a study sponsored by the United States government utilizing skin painting techniques conceded "the uncertain relationship between tumors resulting from mouse skin painted with condensate and human lung cancer."⁶ Consequently, such experiments have been characterized as involving applying "the wrong material in the wrong form, in the wrong dosage, to the wrong tissue of the wrong animal."⁷

It is misleading, therefore, to draw definitive conclusions about "tar" and human disease from skin painting studies. As a knowledgeable observer of research in this area has stated: "Bronchogenic carcinoma [lung cancer] has never been produced by tobacco or its products in any experimental animal despite the multiplicity of attempts."⁸ (Emphasis added) All in all, the following statement made in the mid-1970's still provides a concise summary of the current state of scientific data concerning "tar":

Human beings do not smoke 'tar' and laboratory reports on 'tar' yields have not been established as significant to human health.

B. Nicotine

Nicotine is a natural element of tobacco and, thus, is present in tobacco smoke. Nicotine has been described by some researchers as having no known chronic or cumulative effects on human health.¹⁰ The data on the nature of nicotine's relationship to human health is inconclusive at best, because, among other things, science cannot determine with any precision how much nicotine a smoker is exposed to. In fact, no correlation between the nicotine level of a cigarette or the number of cigarettes smoked and the smoker's actual nicotine intake has been conclusively established because of individual variations in puff rates, depth of inhalation, and body metabolism.¹¹

Nonetheless, anti-smoking advocates blame nicotine for the development of heart disease. Yet no biological mechanism by which nicotine, or any other agent, may be involved in heart disease has been demonstrated. Serious questions about what role, if any, nicotine plays have been raised as a result of autopsy findings of fatty deposits and other changes in the arteries of individuals who either have not smoked or could have smoked only briefly, such as infants, children, and young men killed in military battle.¹² Even the 1983 U.S. Surgeon General's Report, which focused on car-

diovascular disease, concedes that "the evidence for and against a primary role for nicotine in the development or acceleration of atherosclerosis is not conclusive. . . ." ¹³ That opinion was shared by a German researcher who has conducted research on the relationship between nicotine and the clogging of arteries. After reviewing the literature, he and his co-author concluded that "there is no established evidence which supports the hypothesis that nicotine has any influence on the development" of those changes. ¹⁴ (Emphasis added)

Claims by anti-smoking advocates regarding the role of nicotine in the development of heart disease are further undermined by two epidemiological (population) studies. In a study that dealt with myocardial infarction (heart attack), the authors reported finding -- contrary to what they expected -- that the nicotine and carbon monoxide levels of the cigarettes their subjects smoked were not related to the risk of heart attack. ¹⁵

The second study, chaired by a well-known British scientist opposed to cigarette smoking, examined the serum (blood) levels of cotinine, a nicotine metabolite, in male nonsmokers and smokers of cigarettes only, cigars only, and pipes only. The study determined that the mean cotinine level for pipe smokers was significantly higher than the levels for cigarette and cigar smokers. Since studies of pipe smokers generally have not reported an increased risk of coronary heart disease, the researchers concluded

that "nicotine is unlikely to be the major cause of the excess coronary heart disease mortality in cigarette smokers."¹⁶ After re-evaluating their methodology in response to anti-smoking criticism of their study, the researchers again concluded that they were "reasonably confident" that "exposure to high systemic concentrations of nicotine is not a cause of the disease." Although the researchers quibbled with the result of their own study, arguing that their data "cannot completely exonerate" nicotine, they added that the data do "substantially reduce the weight of evidence suggesting that nicotine is a cause of coronary heart disease."¹⁷

Animal studies which purport to establish a causal role for nicotine in heart disease have been soundly criticized for their unrealistic and excessive test conditions. An American researcher who conducted animal studies on this subject has noted:

There have been some studies that have exhibited minor or questionable changes with the use of an equivalent dose of 600 or more cigarettes a day in man. This is such a large number that I think man would find it difficult to find the time to smoke them.¹⁸

In contrast, this researcher concluded that animal studies using realistic doses of nicotine have "failed to initiate, exacerbate, or otherwise influence" the process leading to the clogging of arteries in test animals.¹⁹ In one such study, which was funded by the United States government, male beagle dogs fed a special diet to induce this process were exposed for two years to cigarette

smoke containing low or high levels of nicotine and, in some cases, enriched with carbon monoxide. According to the final report of the research laboratory which conducted the study, "the results of this study lent no support to the suggestion that cigarette smoking increases the rate of development" of this process.²⁰

The foregoing demonstrates the validity of one researcher's summary: "While many studies have been done in this field, none have established nicotine as contributing to the causation, aggravation or precipitation of any cardiovascular disease."²¹ (Emphasis added)

C. Carbon Monoxide

Carbon monoxide (CO) is a tasteless, odorless, colorless gas produced by many natural and man-made sources, including automobile exhaust and industrial emissions. It is naturally produced by the body during daily metabolism. Burning cigarettes also produce CO, but that amount has been described as "insignificant" compared to most other sources.²² Nonetheless, CO has received considerable attention in the scientific literature, usually in regard to cardiovascular disease (CVD). In a review of such literature, however, two public health specialists concluded that "despite the large amount of literature available, the conclusions that can be drawn as to the role of CO in human CVD remain tentative and open to varying interpretations."²³ This conclusion is supported

by a similar statement in the 1983 U.S. Surgeon General's Report, which focused on heart disease:

Carbon monoxide is another major component of cigarette smoke for which there are some data supporting a possible atherogenic [plaque forming inside the arteries] role; however, a review of recent literature on the role of carbon monoxide in arterial injury and atherogenesis leads to no consensus.²⁴

The conclusion of another group which also reviewed the literature was more concise. The chairman of the American Heart Association Task Force on Environment and the Cardiovascular System reported that his group had concluded that the question of whether CO causes heart disease "remains unanswered even at the basic science level."²⁵ (Emphasis added)

Specialists who reviewed these and other studies have concluded that "there is no evidence" to support the suggestion that exposure to low or moderate levels of CO increases the rate of development of atherosclerotic disease in man. Indeed, they contend that "sufficient evidence is available to support the conclusion that, in fact, CO is not of pathogenetic [disease causing] consequence in atherosclerotic disease."²⁶ (Emphasis added)

D. Other Constituents*

Over the years, the principal focus of the attention and concern of smoking critics has been on "tar," nicotine and CO. One researcher who has tried to establish a causal link between smoking and disease, however, concluded with reference to these substances that:

We assume that it is the tar which causes lung cancer, but we do not know this for certain.

Until now, we have implicated nicotine in the development of cardiovascular diseases, but we cannot prove this.

The same is true for CO.²⁷

Thus, some anti-smoking advocates have attempted to shift public attention to the presence of other substances in cigarette smoke. These substances, as found in cigarette smoke (like "tar," nicotine, and CO), have not been scientifically proven to cause any disease in humans. Nonetheless, these constituents are of interest because at levels and under conditions of exposure greatly different than those encountered by the smoker, certain of these compounds may have a toxic effect on or may be associated with disease in animals or humans.

* A more detailed discussion of specific constituents appears in Appendix A to this paper.

It is an axiom among toxicologists that any substance is toxic if the level of exposure is high enough and no substance is toxic if the level of exposure is low enough.²⁸ The amount of substances other than nicotine and CO in cigarette smoke is extremely low, measured in terms of micrograms and nanograms per cigarette. As previously noted, a microgram is one-millionth of a gram, the equivalent of one second in twelve days. A nanogram is one billionth of a gram, the equivalent of one second in thirty-two years.

Moreover, these substances are for the most part natural by-products of combustion of any organic matter, including tobacco, or are found in any organic matter whether or not that matter is burned. Likewise, other compounds present in smoke are also present in the air we breathe and the water we drink. Thus, it is scientifically inaccurate to state as "fact" that there is something "unique" about the presence of these substances in cigarette smoke.

III. CONCLUSION

Numerous claims have been made about the relationship between cigarette smoke constituents and the health of the smoker. However, such claims are just that -- claims which are not supported by reliable scientific proof. After years of study, no scientific relationship has been established between "tar," nicotine and carbon monoxide and human disease. Other constituents, detectable at extremely low levels in cigarette smoke, are the subject of occa-

sional public comment. These substances are not unique to tobacco smoke, however, and as with "tar," nicotine and CO, have not been proven to cause disease in humans in the form in which they are found in cigarette smoke.

REFERENCES

1. Okun, R., Statement, Re: "Cigarette Smoking and Disease, 1976." In: Hearings Before the Committee on Labor and Public Welfare, Subcommittee on Health, United States Senate, Ninety-Fourth Congress, Second Session, 152-167 (at 155), February 19, March 24, and May 27, 1976.
2. U.S. Department of Health, Education and Welfare, Public Health Service, Center for Disease Control, "Chapter 12. Harmful Constituents of Cigarette Smoke," The Health Consequences of Smoking: A Reference Edition, HEW Publication No. (CDC) 78-8357, Washington, D.C., U.S. Government Printing Office, 621-634 (at 625), 1976.
3. Schönherr, H., Klimisch, H.-J., and Harke, H.-P., "Alterung von Zigarettenrauchkondensat: Quantitative Untersuchungen der Artefaktbildung durch Gas- und Partikelphasenreaktionen (Aging of Cigarette Smoke Condensate: Quantitative Investigation of Artifact Formation Via Gas and Particle Phase Reactions)," Beiträge zur Tabakforschung 7(1): 18-23, January, 1973. Translation.

Dube, M.F. and C.R. Green, "Methods of Collection of Smoke for Analytical Purposes." In: Recent Advances in Tobacco Science, Published Proceedings of The 36th Tobacco Chemists' Research Conference, Volume 8, 42-102, October 25, 1982.
4. Hine, C.H., Statement, Re: "Cigarette Smoking and Disease, 1976." In: Hearings Before the Committee on Labor and Public Welfare, Subcommittee on Health, United States Senate, Ninety-Fourth Congress, Second Session, 127-145 (at 138), February 19, March 24 and May 27, 1976.
5. Macdonald, I.G., Statement, Re: "False and Misleading Advertising (Filter-Tip Cigarettes)." In: Hearings Before the Committee on Government Operations, Subcommittee on Legal and Monetary Affairs, United States House of Representatives, Eighty-Fifth Congress, First Session, 224-240, July 18, 19, 23, 24, 25 and 26, 1957.

Hockett, R.C., Statement, Re: "Public Health Cigarette Amendments of 1971." In: Hearings Before the Committee on Commerce, Consumer Subcommittee, United States Senate, Ninety-Second Congress, Second Session, 97-122 (at 102), February 1, 3, and 10, 1972.
6. U.S. Department of Health, Education and Welfare, Public Health Service, National Institutes of Health, National Cancer Institute Smoking and Health Program, Report No. 5: Toward

Less Hazardous Cigarettes. Summary: Four Skin Painting Bioassays Using Condensate From Experimental Cigarettes, 1-29 (at 2), September, 1980.

7. Hockett, R.C., Statement, Re: "Public Health Cigarette Amendments of 1971." In: Hearings Before the Committee on Commerce, Consumer Subcommittee, United States Senate, Ninety-Second Congress, Second Session, 97-122 (at 102), February 1, 3, and 10, 1972.

Hockett, R.C., Statement, Re: "Comprehensive Smoking Prevention Education Act." In: Appendix to Hearings Before the Committee on Energy and Commerce, Subcommittee on Health and the Environment, United States House of Representatives, Ninety-Seventh Congress, Second Session, 627-635 (at 635), March 5, 11 and 12, 1982.

8. Hockett, R.C., Statement, Re: "Comprehensive Smoking Prevention Education Act." In: Hearings Before the Committee on Energy and Commerce, Subcommittee on Health and the Environment, United States House of Representatives, Ninety-Eighth Congress, First Session, 841-851 (at 844), March 9 and 17, 1983.

9. Okun, R., Statement, Re: "Cigarette Smoking and Disease, 1976." In: Hearings Before the Committee on Labor and Public Welfare, Subcommittee on Health, United States Senate, Ninety-Fourth Congress, Second Session, 152-167 (at 154), February 19, March 24, and May 27, 1976.

10. Hockett, R.C., Statement, Re: "Cigarette Smoking and Disease, 1976." In: Hearings Before the Committee on Labor and Public Welfare, Subcommittee on Health, United States Senate, Ninety-Fourth Congress, Second Session, 146-151, February 19, March 24, and May 27, 1976.

Hine, C.H., Statement, Re: "Cigarette Smoking and Disease, 1976." In: Hearings Before the Committee on Labor and Public Welfare, Subcommittee on Health, United States Senate, Ninety-Fourth Congress, Second Session, 127-145, February 19, March 24 and May 27, 1976.

11. Langone, J.J., Gjika, H.B. and Van Vunakis, H., "Nicotine and Its Metabolites. Radioimmunoassays for Nicotine and Cotinine," Biochemistry 12(24): 5025-5030, 1973.

12. Benditt, E.P., "The Origin of Atherosclerosis," Scientific American 236(2): 74-85, February, 1977.

Blumenthal, S., Jesse, M.J., Hennekens, C.H., Klein, B.E., Ferrer, P.L. and Gourley, J.E., "Risk Factors for Coronary

Artery Disease in Children of Affected Families," The Journal of Pediatrics 87(6, Pt. 2): 1187-1192, December, 1975.

Newman, W.P., Freedman, D.S., Voors, A.W., Gard, P.D., Srinivasan, S.R., Cresanta, J.L., Williamson, G.D., Webber, L.S. and Berenson, G.S., "Relation of Serum Lipoprotein Levels and Systolic Blood Pressure to Early Atherosclerosis: The Bogalusa Heart Study," New England Journal of Medicine 314(3): 138-144, January 16, 1986.

Rifkind, B.M. and Lenfant, C., "Cholesterol Lowering and the Reduction of Coronary Heart Disease Risk," Journal of the American Medical Association 256(20): 2872-2873, November 28, 1986.

Strong, J.P., "Coronary Atherosclerosis in Soldiers: A Clue to the Natural History of Atherosclerosis in the Young," Journal of the American Medical Association 256(20): 2863-2866, November 28, 1986.

Enos, W.F., Holmes, R.H. and Beyer, J., "Coronary Disease Among United States Soldiers Killed in Action in Korea: Preliminary Report," Journal of the American Medical Association 152(12): 1090-1093, July 18, 1953.

Enos, W.F., Beyer, J.C. and Holmes, R.H., "Pathogenesis of Coronary Disease in American Soldiers Killed in Korea," Journal of the American Medical Association 158(11): 912-914, July 16, 1955.

Enos, W.F., Holmes, R.H. and Beyer, J.C., "Pathology of Coronary Arteriosclerosis," The American Journal of Cardiology 9(3): 343-354, March, 1962.

McNamara, J.J., Molot, M.A., Stremple, J.F. and Cutting, R.T., "Coronary Artery Disease in Combat Casualties in Vietnam," Journal of the American Medical Association 216(7): 1185-1187, May 17, 1971.

13. U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health, "Section 2. Arteriosclerosis," The Health Consequences of Smoking: Cardiovascular Disease. A Report of the Surgeon General: 1983, DHHS Publication No. (PHS) 84-50204, Washington, D.C., U.S. Government Printing Office, 13-62 (at 50), 1983.
14. Schievelbein, H. and Heinemann, G., "Nicotine and Atherosclerosis." In: Atherosclerosis VI: Proceedings of the Sixth International Symposium, F.G. Schettler, A.M. Gotto, G. Middelhoff, A.J.R. Hablnicht and K.R. Jurutka (eds.). Berlin, Springer-Verlag, 899-902 (at 901), 1983.

15. Kaufman, D.W., Helmrich, S.P., Rosenberg, L., Miettinen, O.S. and Shapiro, S., "Nicotine and Carbon Monoxide Content of Cigarette Smoke and the Risk of Myocardial Infarction in Young Men," The New England Journal of Medicine 308(8): 409-413, February 24, 1983.
16. Wald, N.J., Idle, M. and Boreham, J., "Serum Cotinine Levels in Pipe Smokers: Evidence Against Nicotine as Cause of Coronary Heart Disease," The Lancet II(8250): 775-777 (at 775), October 10, 1981.
17. Wald, N.J., Idle, M., Boreham, J., Bailey, A and Van Vunakis, H., "Urinary Nicotine Concentrations in Cigarette and Pipe Smokers," Thorax 39(5): 365-368 (at 368), 1984.
18. Fisher, E.R., Statement, Re: "Smoking Prevention Education Act." In: Hearings Before the Committee on Energy and Commerce, Subcommittee on Health and the Environment, United States House of Representatives, Ninety-Eighth Congress, First Session, 406-423 (at 407), March 9 and 17, 1983.
19. Fisher, E.R., Statement, Re: "Smoking Prevention Education Act." In: Hearings Before the Committee on Energy and Commerce, Subcommittee on Health and the Environment, United States House of Representatives, Ninety-Eighth Congress, First Session, 406-423 (at 407), March 9 and 17, 1983.
20. Hazleton Laboratories America, Inc., Final Report. Inhalation Bioassay of Cigarette Smoke in Dogs: Effects of Nicotine and Carbon Monoxide on Atherogenesis, Project No. 976-904, Contract No. ECI-SHP-75-112, Submitted to the National Cancer Institute, Division of Cancer Cause and Prevention, Smoking and Health Program, Washington, D.C., 1-31 (at 5-6), June 10, 1981.
21. Hockett, R.C., Statement, Re: "Cigarette Smoking and Disease, 1976." In: Hearings Before the Committee on Labor and Public Welfare, Subcommittee on Health, United States Senate, Ninety-Fourth Congress, Second Session, 146-151 (at 147), February 19, March 24, and May 27, 1976.
22. Wakeham, H.R.R., "Environmental Carbon Monoxide from Cigarette Smoking -- A Critique," Preventive Medicine 6: 526-534 (at 526), 1977.
23. Weir, F.W. and Fabiano, V.L., "Re-Evaluation of the Role of Carbon Monoxide in Production or Aggravation of Cardiovascular Disease Processes," Journal of Occupational Medicine 24(7): 519-525 (at 520), July, 1982.
24. U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health, "Section 2.

Arteriosclerosis," The Health Consequences of Smoking: Cardiovascular Disease. A Report of the Surgeon General: 1983, DHHS Publication No. (PHS) 84-50204, Washington, D.C., U.S. Government Printing Office, 13-62 (see particularly 51), 1983.

25. Gonzalez, E.R., "No Proof of Environmental Ill Effects on Heart," Journal of the American Medical Association 243(12): 1219-1220 (at 1219), March 28, 1980.
26. Weir, F.W. and Fabiano, V.L., "Re-Evaluation of the Role of Carbon Monoxide in Production or Aggravation of Cardiovascular Disease Processes," Journal of Occupational Medicine 24(7): 519-525 (at 523), July, 1982.
27. Astrup, P., Quoted in "Zigaretten, Nikotin und Kohlenmonoxid. Wie kann man Raucherschäden mindern? (Cigarettes, Nicotine and Carbon Monoxide. How Can Harm to Smokers Be Reduced?)," UMSCHAU 79(1): 11-18, 1979. Translation, p. 21.
28. Doull, J. and Bruce, M.C., "Chapter 1. Origin and Scope of Toxicology." In: Casarett & Doull's Toxicology. The Basic Science of Poisons. Third Edition. New York, Macmillan Publishing Company, 3-10 (see particularly 3), 1986.

APPENDIX A

OTHER CONSTITUENTS

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I. INTRODUCTION

The following is a brief discussion of other constituents in cigarette smoke sometimes referenced by anti-smokers. As stated previously, the vast majority of such constituents, some of which have been identified in "tar," are present in cigarette smoke only in extremely small amounts. As is the case with "tar," nicotine and CO, these minute subfractions of tobacco smoke have not been scientifically proven to cause human disease as they are encountered by the smoker.

II. OTHER CONSTITUENTS

Acetaldehyde

Acetaldehyde is reportedly present in cigarette smoke in minute quantities. It is a chemical compound related to ethanol and is used in the manufacture of plastics and synthetic rubber. Acetaldehyde is also commonly found in perfume.¹ Exposure to extremely high levels of acetaldehyde has an eye and skin irritant effect, and may be toxic.² However, an international research group recently concluded that the data was "inadequate" to support any claim that acetaldehyde causes cancer in humans at any level of exposure.³

Acetone

Acetone has been reported to be present in minute quantities in the "vapor phase" of cigarette smoke, i.e., it is not found in "tar" (smoke condensate). It is most commonly encountered either at work or at home in the form of cleaning solvent. It has

also been detected in freeze-dried foods and dried milk. Moreover, acetone is a naturally occurring constituent of human blood and urine.⁴

Acetone is not considered toxic at low levels of exposure, although at higher levels of exposure it can be an eye or skin irritant.⁵ One researcher reported that he was unable to produce tumors through the mouse-skin painting method using acetone.⁶

Acrolein

Acrolein has been reported to be present in small quantities in the vapor phase of cigarette smoke. It is also everywhere in the environment as a product of fires, automobile exhaust, and other industrial emissions. Acrolein is also produced by burning foods containing fat, such as grilling a steak.⁷ Although at high concentrations acrolein may have a toxic or irritant effect, one recent review of the research conducted regarding acrolein's toxicity or carcinogenicity in humans concluded "there is no evidence to support that acrolein is a human carcinogen."⁸

Ammonia

Ammonia is reportedly detectable in minute amounts in cigarette smoke. It occurs naturally as a part of protein metabolism in man and in virtually all species of animals. Ammonia is widely used as a fertilizer. It is also a common household cleanser.⁹ At high concentrations, ammonia can have a strong irritant

effect and cause burns; its pungent odor, of course, is very familiar. One researcher, however, recently noted that:

The biologic significance of inhaled ammonia in the concentrations generated in mainstream smoke, which are very low, is purely conjectural.¹⁰

Arsenic

Arsenic is a naturally occurring metal that is drawn into growing tobacco (and other plants) from the soil. It is present also in rocks, water, and virtually all living organisms in concentrations of parts per million and parts per billion. The United States government has estimated that non-smokers generally take in up to 60 micrograms of arsenic per day from various sources; it has also estimated that smokers take in an additional two micrograms of arsenic per pack of cigarettes smoked, thus increasing their daily arsenic intake only marginally.¹¹ One recent literature review noted that over 99% of the arsenic (and other metals such as lead and cadmium) in tobacco remains in cigarette ash.¹²

Analyses of the literature regarding the relationship between exposure to arsenic and disease have generally been inconclusive. For example, in a recent review of the literature, a researcher characterized "its claimed effects on human smokers as speculative."¹³ The 1982 U.S. Surgeon General's Report also noted that "the view that inorganic arsenicals cause cancer of the skin and lung has not been widely accepted. . . ."¹⁴

Benzene

Benzene has been reported to be present in the vapor phase of cigarette smoke in small quantities. Although benzene has sometimes been suggested as a possible cause of leukemia, leukemia has not been consistently related to cigarette smoking in the various statistical studies that form the primary basis for public health criticism of smoking.¹⁵ The U.S. Surgeon General has also noted that "no dose-response relationship has been established between death rate from leukemia and number of cigarettes smoked."¹⁶

Benzo(a)pyrene

Benzo(a)pyrene (BaP) is sometimes singled out as a possible human carcinogen because it is a component of the laboratory product "tar;" "tar," as noted above, can produce tumors under the highly artificial conditions involved in animal skin painting experiments. Claims that BaP, and other polycyclic aromatic hydrocarbons (such as dibenzacridine), can cause cancer in humans thus suffer from the same weaknesses as those claims generally directed at "tar."

BaP is formed by the incomplete combustion of organic matter. In addition to cigarette smoke, other sources of BaP in the atmosphere are coal and oil fired power stations, domestic heating, industrial processes and emissions, automobile emissions, and forest fires and volcanic activity. Atmospheric BaP is carried into the soil, the water table, and the ocean through rainfall. Thus, BaP is detectable in fish, meat and vegetables, as well as

in drinking water. Foodstuffs as varied as coconut oil, sardines, and cheese all contain BaP at relatively high levels. Charcoal-grilled meats have been reported to contain particularly high levels of BaP.¹⁷ Two researchers concluded that the BaP concentration in a single charcoal-grilled steak was equivalent to that in the smoke of 600 cigarettes.¹⁸ The daily levels of exposure to BaP simply from breathing the air in some cities has been estimated, by a former U.S. Surgeon General, to be approximately twice as high as that for a cigarette smoker.¹⁹

Butane

Butane may be present in the vapor phase of cigarette smoke in minute quantities. It occurs in natural gas and is present in the atmosphere as the result of the combustion of gasoline and other petroleum products. Butane is also frequently used as an aerosol propellant. The inhalation of butane has not been demonstrated to produce disease in humans.²⁰

Cadmium

Cadmium is a trace "heavy metal" that has been reported to be present in tobacco and in cigarette smoke in certain compound forms. It is used extensively in the production of cadmium-copper alloys and corrosion-resistant coatings. It is found in alkaline batteries, glass, solder, paint pigments and some pesticides and fungicides. The principal sources of cadmium exposure for man are in food, dairy products and drinking water.²¹

It has been estimated that in most countries the average smoker is exposed to approximately the same amount of cadmium daily through smoking as he or she is through diet.²² Other researchers recently concluded that the amount of cadmium in two packs of cigarettes, even if entirely inhaled, would still be less than would be inspired in two hours of breathing atmospheric cadmium at the maximum safe levels established by the health authorities of several countries.²³

Cadmium has been identified as a possible tumor promotor under experimental conditions in animals. Three German researchers recently observed, however, that the results of these experiments should not be extrapolated to humans because the doses necessary to induce tumor production corresponded to smoking between 5,000 to 20,000 cigarettes per day.²⁴ Similarly, a recent review of the literature concerning the claimed carcinogenicity of cadmium noted that "evidence for potential cadmium carcinogenicity in humans in the dosages delivered from smoking is very limited."²⁵

Chromium

Chromium is a metal that is reportedly detectable in trace amounts in tobacco. Like the other trace metals in tobacco, it is drawn into the growing plant from the soil. Also like the other metals in tobacco, it is estimated by one researcher that over 99% of the chromium in tobacco remains in cigarette ash and is not transferred into smoke.²⁶ A group of researchers recently concluded that "[t]here is no indication . . . that the chromium

[in tobacco] goes to the mainstream smoke."²⁷ (Emphasis added)

Chromium is a naturally occurring element of rock; as rock is weathered into soil, the chromium is transferred into the soil as well. From the soil, chromium is both washed into the oceans, where it is incorporated into the oceanic food-chain, and it is taken up by growing plants and incorporated into the land food-chain. Chromium compounds are also present in the atmosphere as a result of industrial emissions of the burning of organic matter.²⁸ Food is the principal environmental source of chromium intake by man, with vegetables, unrefined sugar, beef, liver, eggs and animal fats generally having the highest concentrations.²⁹

Studies of various illnesses developed by workers in the chromate industry, who were exposed to large concentrations of chromium compounds over many years, have raised concerns about chromium as a possible cause of chronic disease in humans.³⁰ These studies have been subject to scientific criticism.³¹ Given the extremely low level, if any, to which a smoker is exposed to chromium beyond his or her normal dietary and environmental chromium intake, according to one researcher "its role as a potential carcinogen in human smokers is not known."³²

Hydrogen Cyanide

Hydrogen cyanide (HCN) is also reportedly present in minute amounts in the vapor phase of cigarette smoke. It is produced by the combustion of the amino acids in tobacco. HCN is also generated by the combustion of carbon materials in air, for

example, during home cooking. HCN is used in a variety of industrial processes and is also present in such varied food products as bitter almonds, lima beans, soybeans, apricots, and linseed. It has been detected in certain wines.³³

A recent study noted that although the HCN level detectable in smokers' blood is slightly elevated after smoking, it is rapidly eliminated from the system.³⁴ Another reviewer concluded that the effect of HCN in cigarette smoke, if any, on humans "remains to be determined."³⁵

Lead

Lead, like the other trace metals reportedly present in tobacco, is drawn from the soil into the growing plant. Also like the other trace metals, one researcher estimated that less than one percent of the lead in the tobacco is transferred to the smoke, with the remainder left in the ash.³⁶ Lead is present in the air, soil and water. Hence, smokers and non-smokers alike are exposed to and ingest small amounts of lead each day. One research group has estimated that a smoker will ingest five micrograms of lead from a pack of cigarettes; the dietary intake of lead per day, however, has been reported to be much higher.³⁷

Numerous health concerns have been expressed regarding exposure to high levels of lead and lead compounds. However, given the very low levels of lead exposure from tobacco, one researcher concluded that "the role of lead as a potential carcinogen for human smokers is not known."³⁸

Methanol

Methanol is reported to be present in very small quantities in cigarette smoke as a vapor phase component. It is used in enamels, dyes, stains, cleaning solvents, paint and varnish removers, antifreeze mixtures, and as fuel for internal combustion engines. It is also present in bread, soy sauce and various fruits and vegetables.³⁹

Methanol can be a skin and eye irritant in large concentrations. One researcher recently noted, however, that "[c]onsidering the dose of methanol estimated to be toxic to humans (1 g/kg), it is unlikely that a normal human being could ever be exposed to enough of it by inhalation to experience acute toxicity."⁴⁰ This scientist also noted that he had been unable to find any studies showing the inhalation of methanol to be carcinogenic.

Naphthalene

Naphthalene is a substance related to benzene. It is reportedly present both in "tar" and in the vapor phase of cigarette smoke in small quantities, and is generated by the combustion of tobacco. Naphthalene is used extensively in the chemical, plastics and dye industries. In the home, it is found frequently in air fresheners, moth balls, varnishes and wood preservatives. Radishes also contain naphthalene.⁴¹ Naphthalene has no conclusive reported carcinogenic effect, although it is sometimes associated with leu-

kemia in animal experiments. As noted above, leukemia has not been consistently statistically associated with cigarette smoking.⁴²

Nickel

Nickel, like arsenic, is drawn from the soil into growing tobacco. Also like arsenic, it is estimated that 99% of the nickel in tobacco remains in the ash of a cigarette, and is not transferred to the smoke. The U.S. Surgeon General has concluded that "it is not likely that nickel plays a significant role in the etiology of lung cancer in cigarette smokers. . . ."⁴³ Other researchers and reviewers have reached the same conclusion.⁴⁴

Nitrogen Oxides

Cigarette smoke reportedly contains nitric oxide (NO), but "very little, if any," nitrous oxide or nitrogen dioxide.⁴⁵ The U.S. Surgeon General has noted data showing that both smokers and nonsmokers maintain "a consistently low level" of NO in their blood and has suggested that the "lack of a significant difference" between the two groups indicates that NO from external sources "appears to have little effect" on the amount found in the blood.⁴⁶

Nitrosamines

Nitrosamines reportedly are detectable in both "tar" and in the vapor phase component of cigarette smoke. The presence of nitrosamines in cigarette smoke is often the subject of public comment by anti-smoking advocates because, under experimental con-

ditions, certain nitrosamine compounds can produce tumors in laboratory animals. As two reviewers of the literature noted, however, "direct epidemiologic evidence that would associate nitrosamines with human cancer is very limited."⁴⁷ Another recent reviewer suggested that:

The role of nitrosamines in the pathogenesis of human lung cancers is theoretical, and it is yet to be shown conclusively that any specific N-nitroso compound causes human cancer.⁴⁸

Even the U.S. Surgeon General has stated that there is "a lack of direct evidence" that the nitrosamines specific to tobacco have any proven health effect on smokers.⁴⁹

The components of nitrosamines -- nitrates, nitrites and amines -- are naturally occurring substances. Hence, nitrosamines are found in soil, air, water and food. Beer and scotch whiskey have recently been determined to contain dimethylnitrosamine.⁵⁰ Foods often prepared with nitrites (used as a preservative) include ham, sausages, bacon, luncheon meats and frankfurters; seafood and cheese also often contain nitrosamines.⁵¹

Phenol

Phenol is reported to be present in minute quantities in cigarette smoke and is detectable in "tar." It has a variety of industrial uses, including the manufacture of perfumes, plastics and fertilizers. Phenol occurs naturally in animal tissues; the consumption of meat has been identified as the primary source of human exposure to phenol. It is also present in drinking water.⁵²

Two reviewers of the literature concluded that "[t]here is no specific evidence of human cancer attributable to phenol or related compounds. . . ."⁵³ A group of researchers likewise reported that phenol is not present in cigarette smoke at high enough concentrations to cause disease in smokers.⁵⁴

Polonium-210

Polonium-210 is a radioactive element that has been reported to be present in trace amounts in tobacco and cigarette smoke. It is also present in the atmosphere and in soil -- both as a part of the earth's natural background radiation and as a result of nuclear testing -- from which it is presumably drawn into growing tobacco. Smoking critics often cite the presence of polonium-210 in smoke as significant because it, along with most other radioactive materials, can have adverse health effects in humans and in animals if the exposure is of sufficient intensity. Even the U.S. Surgeon General, however, has questioned the significance of polonium-210 to lung cancer in humans.⁵⁵ Other researchers have disputed the conclusion drawn by some scientists that polonium-210 accumulates in the lung tissue of smokers.⁵⁶ Additional researchers discount the claimed risk to smokers of inhaled polonium, noting the extraordinarily minute quantities at which it is present.⁵⁷

Toluene

Toluene is reported to be a constituent of the vapor phase component of cigarette smoke. It is present in the atmosphere as a result of industrial emissions, automobile emissions, and gasoline evaporation. Exposures at home include inks, dyes, and perfumes.⁵⁸ Although it is an eye and skin irritant at low levels and concentrations, toluene has not been reported to be toxic or to cause chronic disease in humans at those levels.⁵⁹

Urethane

Urethane (ethyl carbamate) has been reported to be present in cigarette smoke in very small amounts. It has been widely used in the plastics and textile industries. It is also used in a variety of agricultural chemicals, pesticides, fungicides, and in some therapeutic drugs. Urethane is a natural by-product of fermentation, and is found in wines, distilled spirits, and beer, as well as in fermented food products such as cheese, yogurt and soy sauce.⁶⁰ The U.S. Surgeon General has conceded that urethane, although possibly an animal carcinogen, is not present in cigarette smoke in sufficient quantities to cause cancer in smokers.⁶¹

Vinyl Chloride

Vinyl chloride is reportedly present in minute amounts in the vapor phase of cigarette smoke. Although it is a gas, it is detectable in various food products such as honey, butter and tomato ketchup. It is also present in some wines.⁶² Vinyl chloride

is also used in the manufacture of plastics.⁶³

Vinyl chloride has been reported to have toxic and carcinogenic effects in animals at high concentrations; a similar effect on humans has been suggested. One group of oncologists, however, although subscribing to the general theory that smoking causes cancer, conceded that:

Based on human data and results from animal studies, it appears to us that the[] minute amounts of [vinyl chloride in cigarette smoke] will not contribute to a measurable degree to the carcinogenic activity of tobacco smoke.⁶⁴

This conclusion was echoed by a recent literature reviewer, who concluded that vinyl chloride is present in cigarette smoke "apparently at levels too low to be considered a carcinogen or fibrosis-inducing agent."⁶⁵

REFERENCES

1. "Hazardous Materials: Acetaldehyde," Dangerous Properties of Industrial Materials Report 9(6): 30-45, 1989.
2. "Hazardous Materials: Acetaldehyde," Dangerous Properties of Industrial Materials Report 9(6): 30-45, 1989.

Brabec, M.J., "Chapter Thirty-Seven. Aldehydes and Acetals." In: Patty's Industrial Hygiene and Toxicology. Third Revised Edition. G.D. Clayton and F.E. Clayton (eds.). New York, John Wiley & Sons, 2629-2669 (see particularly 2633, 2646), 1982.
3. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, "Acetaldehyde (Group 2B)," IARC Monographs On the Evaluation of Carcinogenic Risks to Humans. Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42. Supplement 7, 77-78 (at 77), 1987.
4. Krasavage, W.J., O'Donoghue, J.L., and DiVincenzo, G.D., "Ketones." In: Chapter Fifty-Six. Patty's Industrial Hygiene and Toxicology. Third Revised Edition. G.D. Clayton and F. E. Clayton (eds.). New York, John Wiley & Sons, 4709-4800 (see particularly 4726), 1982.

Kayaert, G., Tobback, P., Maes, E., Flink, J. and Karel, M., "Retention of Volatile Organic Compounds in a Complex Freeze-Dried Food Gel," Journal of Food Technology 10(1): 11-18, 1975.

Maier, H.G., "Zur Bindung flüchtiger Aromastoffe an Lebensmittel. VI. Mitteilung. Einfache Ketone (Binding of Volatile Aroma Constituents in Foods. VI. Continuation. Simple Ketones)," Zeitschrift Für Lebensmittel -Untersuchung und -Forschung 149(2): 65-69, 1972. English Summary.
5. Krasavage, W.J., O'Donoghue, J.L., and DiVincenzo, G.D., "Ketones." In: Chapter Fifty-Six. Patty's Industrial Hygiene and Toxicology. Third Revised Edition. G.D. Clayton and F. E. Clayton (eds.). New York, John Wiley & Sons, 4709-4800 (see particularly 4724-4726), 1982.
6. Bock, F.G., Swain, A.P. and Stedman, R.L., "Composition Studies on Tobacco. XLI. Carcinogenesis Assay of Subfractions of the Neutral Fraction of Cigarette Smoke Condensate," Journal of the National Cancer Institute 44(6): 1305-1310, 1970.
7. Beauchamp, R.O., Andjelkovich, D.A., Kligerman, A.D., Morgan, K.T. and Heck, H.d'A., "A Critical Review of the Literature on

Acrolein Toxicity," CRC Critical Reviews in Toxicology 14(4): 309-380, 1985.

Sakata, T., Smith, R.A., Garland, E.M. and Cohen, S.M., "Rat Urinary Bladder Epithelial Lesions Induced by Acrolein," Journal of Environmental Pathology, Toxicology, and Oncology 9(2): 159-169, 1989.

Feron, V.J., and Kruysse, A., "Effects of Exposure to Acrolein Vapor in Hamsters Simultaneously Treated with Benzo[a]pyrene or Diethylnitrosamine," Journal of Toxicology and Environmental Health 3(3): 379-394, 1977.

8. Beauchamp, R.O., Andjelkovich, D.A., Kligerman, A.D., Morgan, K.T. and Heck, H.d'A., "A Critical Review of the Literature on Acrolein Toxicity," CRC Critical Reviews in Toxicology 14(4): 309-380 (at 342), 1985.
9. Wands, R.C., "Chapter Forty-One. Alkaline Materials: 1. Ammonia, NH_3 , Ammonium Hydroxide, NH_4OH , and Ammonium Salts." In: Patty's Industrial Hygiene and Toxicology. Third Revised Edition. G.D. Clayton and F.E. Clayton (eds.). New York, John Wiley & Sons, 3045-3052, 3067-3069, 1982.
10. Huber, G.L., "Physical, Chemical, and Biologic Properties of Tobacco, Cigarette Smoke, and Other Tobacco Products," Seminars in Respiratory Medicine 10(4): 297-332 (at 316), October, 1989.
11. Stokinger, H.E., "Chapter 29. The Metals: 3. Arsenic, As." In: Patty's Industrial Hygiene and Toxicology. Third Revised Edition. G.D. Clayton and F.E. Clayton (eds.). New York, John Wiley & Sons, 1517-1531, 1982.

Jacobson-Kram, D., Mushak, P., Piscator, M., Sivulka, D.J., Chu, M., Gibb, H.J., Thorslund, T.W. and Crump, K.S., "9. Human Health Risk Assessment for Arsenic," Health Assessment Document for Inorganic Arsenic: Final Report, Washington, D.C., United States Environmental Protection Agency, Office of Health and Environmental Assessment, EPA-600/8-83-021F, 1-11 (at particularly 3-4), March, 1984.

National Academy of Sciences, Committee on Medical and Biologic Effects of Environmental Pollutants, "2. Chemistry of Arsenic." In: Medical and Biologic Effects of Environmental Pollutants: Arsenic. Washington, D.C., National Academy of Sciences, 4-15 (see particularly 4), 1977.

12. Huber, G.L., "Physical, Chemical, and Biologic Properties of Tobacco, Cigarette Smoke and Other Tobacco Products," Seminars in Respiratory Medicine 10(4): 297-332 (see particularly 313), October, 1989.

13. Huber, G.L., "Physical, Chemical, and Biologic Properties of Tobacco, Cigarette Smoke, and Other Tobacco Products," Seminars in Respiratory Medicine 10(4): 297-332 (at 313), October, 1989.
14. U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health, "Part III. Mechanisms of Carcinogenesis: Experimental Carcinogenesis With Tobacco Smoke," The Health Consequences of Smoking: Cancer. A Report of the Surgeon General: 1982, DHHS Publication No. (PHS) 82-50179, Washington, D.C., U.S. Government Printing Office, 181-235 (at 211), 1982.
15. Huber, G.L., "Physical, Chemical, and Biological Properties of Tobacco, Cigarette Smoke, and Other Tobacco Products," Seminars in Respiratory Medicine 10(4): 297-332 (see particularly 312, 316), October, 1989.
16. U.S. Department of Health, Education, and Welfare, Public Health Service, Office on Smoking and Health, "Chapter 14. Constituents of Tobacco Smoke: Benzenes and Naphthalenes," Smoking and Health. A Report of the Surgeon General, DHEW Publication No. (PHS) 79-50066, Washington, D.C., U.S. Government Printing Office, 49, 51 (at 51), 1979.
17. Osborne, M.R. and Crosby, N.T., "Occurrence of Benzopyrenes in the Environment." In: Benzopyrenes. M.M. Coombs, J. Ashby, R.F. Newbold and H. Baxter (eds.). Cambridge, Cambridge University Press, Chapter 17, 301-316, 1987.

Sandmeyer, E.E., "Chapter Forty-Seven. Aromatic Hydrocarbons. 4. Tri- and Polynuclear Ring Systems." In: Patty's Industrial Hygiene and Toxicology. Third Revised Edition. G.D. Clayton and F.E. Clayton (eds.). New York, John Wiley & Sons, 3253-3431 (see particularly 3345), 1982.
18. Lijinsky, W. and Shubik, P., "Benzo(a)pyrene and Other Polynuclear Hydrocarbons in Charcoal-Broiled Meat," Science 145(2): 53-55, 1964.
19. Burney, L.E., "Governmental Responsibilities in Environmental Health," Public Health Reports 76(4): 291-295 (see particularly 293) April, 1961.
20. Sandmeyer, E.E., "Chapter Forty-Five. Aliphatic Hydrocarbons. 1.5. Butanes." In: Patty's Industrial Hygiene and Toxicology. Third Revised Edition. G.D. Clayton and F.E. Clayton (eds.). New York, John Wiley & Sons, 3182-3183, 1982.

Beall, J.R. and Ulsamer, A.G., "Toxicity of Volatile Organic Compounds Present Indoors," Bulletin of The New York Academy

of Medicine 57(10): 978-997 (see particularly 980), December, 1981.

21. Stokinger, H.E., "Chapter Twenty-Nine. The Metals: 7. Cadmium, Cd." In: Patty's Industrial Hygiene and Toxicology. Third Revised Edition. G.D. Clayton and F.E. Clayton (eds.). New York, John Wiley & Sons, 1563-1582, 1982.

Kendrey, G. and Roe, F.J.C., "Cadmium Toxicology," The Lancet, 1206-1207, June 14, 1969.

Gloag, D., "Contamination of Food: Mycotoxins and Metals," British Medical Journal 282(6267): 879-882, March 14, 1981.

22. Lewis, G.P., Jusko, W.J., Coughlin, L.L., and Hartz, S., "Contribution of Cigarette Smoking to Cadmium Accumulation in Man," The Lancet 1(7745): 291-292, February 5, 1972.

Elinder, C.G., Kjellstrom, T., Lind, B., Linnman, L., Piscator, M. and Sundstedt, K., "Cadmium Exposure From Smoking Cigarettes: Variations With Time and Country Where Purchased," Environmental Research 32(1): 220-227, October, 1983.

Scherer, G. and Barkemeyer, H., "Cadmium Concentrations in Tobacco and Tobacco Smoke," Ecotoxicology and Environmental Safety 7(1): 71-78, February, 1983.

Westcott, D.T. and Spincer, D., "The Cadmium, Nickel and Lead Content of Tobacco and Cigarette Smoke," Beiträge zur Tabakforschung 7(4): 217-221, April, 1974.

23. Hennigar, G.R. and Gross, P., "Chapter 5: Drug and Chemical Injury -- Environmental Pathology." In: Anderson's Pathology. J.M. Kissane (ed.). St. Louis, C. V. Mosby Company, Volume 1, 147-238 (see particularly 207), 1985.
24. Schmidt, J.A., Fischbach, E.-D. and Burkart, F., "Cadmium-Untersuchungen im Bereich von Umwelt-, Boden- und Sorteneinflüssen bei Tabak sowie der Cadmium-Übergang in den Zigarettenrauch (A Study of the Influences of Environment, Soil and Varieties on Cadmium Contents in Tobacco and of Cadmium Transfer into Cigarette Smoke)," Zeitschrift für Lebensmittel -Untersuchung und -Forschung 180(4): 306-311, 1985. English Summary and Translation.
25. Huber, G.L., "Physical, Chemical, and Biologic Properties of Tobacco, Cigarette Smoke, and Other Tobacco Products," Seminars in Respiratory Medicine 10(4): 297-332 (at 313), October, 1989.
26. Huber, G.L., "Physical, Chemical, and Biologic Properties of Tobacco, Cigarette Smoke, and Other Tobacco Products," Seminars

in Respiratory Medicine 10(4): 297-332 (see particularly 313), October, 1989.

27. Fan, A.M. and Harding-Borlow, I., "Chromium." In: Advances in Modern Environmental Toxicology. Volume XI. Genotoxic and Carcinogenic Metals: Environmental and Occupational Occurrence and Exposure, L. Fishbein, A. Furst and M.A. Mehlman (eds.). Princeton, Princeton Scientific Publishing Co., Inc., 87-125 (at 89), 1987.
28. WHO Expert Committee on International Programme on Chemical Safety (IPCS), "3. Sources in the Environment, Environmental Transport and Distribution," Environmental Health Criteria 61: Chromium, Geneva, World Health Organization, 32-41, 1988.

Fan, A.M. and Harding-Borlow, I., "Chromium." In: Advances in Modern Environmental Toxicology. Volume XI. Genotoxic and Carcinogenic Metals: Environmental and Occupational Occurrence and Exposure, L. Fishbein, A. Furst and M.A. Mehlman (eds.). Princeton, Princeton Scientific Publishing Co., Inc., 87-125, 1987.
29. Fan, A.M. and Harding-Borlow, I., "Chromium." In: Advances in Modern Environmental Toxicology. Volume XI. Genotoxic and Carcinogenic Metals: Environmental and Occupational Occurrence and Exposure, L. Fishbein, A. Furst and M.A. Mehlman (eds.). Princeton, Princeton Scientific Publishing Co., Inc., 87-125, 1987.
30. Stokinger, H.E., "Chapter Twenty-Nine: The Metals. Section 9, Chromium, Cr." In: Patty's Industrial Hygiene and Toxicology. Third Revised Edition. G.D. Clayton and F. E. Clayton (eds.). New York, John Wiley & Sons, 1589-1605 (see particularly 1601), 1981.
31. Gerhardsson, L., Wester, P.O., Nordberg, G.F. and Brune, D., "Chromium, Cobalt and Lanthanum in Lung, Liver and Kidney Tissue from Deceased Smelter Workers," Science of the Total Environment 37 (2/3): 233-246 (see particularly 242), August 1, 1984.
32. Huber, G.L., "Physical, Chemical, and Biologic Properties of Tobacco, Cigarette Smoke, and Other Tobacco Products," Seminars in Respiratory Medicine 10(4): 297-332 (at 313), October, 1989.
33. Hartung, R., "Chapter Fifty-Eight. Cyanides and Nitriles. 2. Cyanides. 2.1 Hydrogen Cyanide." In: Patty's Industrial Hygiene and Toxicology. Third Revised Edition. G.D. Clayton and F.E. Clayton (eds.). New York, John Wiley & Sons, 4850-4853 (see particularly 4850), 1982.

Honig, D.H., Hockridge, M.E., Gould, R.M. and Rackis J.J., "Determination of Cyanide in Soybeans and Soybean Products," Journal of Agricultural and Food Chemistry 31(2): 272-275, 1983.

Misselhorn, K. and Adam, R., "On The Cyanide Contents in Stone Fruit Products," Branntweinwirtschaft 116(4): 45-50, 1976. English Abstract.

Askar, A. and Morad, M.M., "Lebensmittelvergiftung. 1. Toxine in natürlichen Lebensmitteln (Food Poisoning. 1. Toxins in Natural Foodstuffs)," Alimenta 19: 59-66, 1980. English Summary.

34. Lundquist, P., Rosling, H., Sörbo, B. and Tibbling, L, "Cyanide Concentrations in Blood After Cigarette Smoking, as Determined by a Sensitive Fluorimetric Method," Clinical Chemistry 33(7): 1228-1230, 1987.
35. Huber, G.L., "Physical, Chemical, and Biologic Properties of Tobacco, Cigarette Smoke, and Other Tobacco Products," Seminars in Respiratory Medicine 10(4): 297-332 (at 315), October, 1989.
36. Huber, G.L., "Physical, Chemical, and Biologic Properties of Tobacco, Cigarette Smoke, and Other Tobacco Products," Seminars in Respiratory Medicine 10(4): 297-332 (see particularly 313), October, 1989.
37. IARC Working Group on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, "Lead and Lead Compounds." In: IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Some Metals and Metallic Compounds, Volume 23. Lyon, International Agency for Research on Cancer, 325-416 (see particularly 345, 350-351), 1980.
38. Huber, G.L., "Physical, Chemical, and Biologic Properties of Tobacco, Cigarette Smoke, and Other Tobacco Products," Seminars in Respiratory Medicine 10(4): 297-332 (at 313), October, 1989.
39. Rowe, V.K. and McCollister, S.B., "Chapter Fifty-Six. Alcohols. 2. Methanol." In: Patty's Industrial Hygiene and Toxicology. Third Revised Edition. G.D. Clayton and F.E. Clayton (eds.). New York, John Wiley & Sons, 4528-4541, 1982.

Isshiki, K., "Analysis of Methyl and Ethyl Alcohols in Foods and Assessment of Dietary Intake Levels," Shokuhin Eiseigaku Zasshi (Journal of the Food Hygienic Society of Japan) 26(1): 39-45, 1985. English Abstract.

40. Marnett, L.J., "Health Effects of Aldehydes and Alcohols in Mobile Source Emissions." In: Air Pollution, The Automobile and Public Health. Washington, D.C., National Academy Press, 579-603 (at 587), 1988.
41. Sandmeyer, E.E., "Chapter Forty-Seven. Aromatic Hydrocarbons. 3. Dinuclear Systems. 3.1 Naphthalene." In: Patty's Industrial Hygiene and Toxicology. Third Revised Edition. G.D. Clayton and F. E. Clayton (eds.). New York, John Wiley & Sons, 3333-3343, 3400-3431, 1982.
42. Huber, G.L., "Physical, Chemical, and Biologic Properties of Tobacco, Cigarette Smoke, and Other Tobacco Products," Seminars in Respiratory Medicine 10(4): 297-332 (see particularly 312), October, 1989.
43. U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health, "Part III. Mechanisms of Carcinogenesis: Experimental Carcinogenesis With Tobacco Smoke," The Health Consequences of Smoking: Cancer. A Report of the Surgeon General: 1982, DHHS Publication No. (PHS) 82-50179, Washington, D.C., U.S. Government Printing Office, 181-235 (at 211), 1982.
44. Huber, G.L., "Physical, Chemical, and Biologic Properties of Tobacco, Cigarette Smoke, and Other Tobacco Products," Seminars in Respiratory Medicine 10(4): 297-332 (see particularly 313), October, 1989.
- Wynder, E.L. and Hoffmann, D., Tobacco and Tobacco Smoke: Studies in Experimental Carcinogenesis, New York, Academic Press Inc., 493, 498, 627-628, 1967.
45. Huber, G.L., "Physical, Chemical, and Biologic Properties of Tobacco, Cigarette Smoke, and Other Tobacco Products," Seminars in Respiratory Medicine 10(4): 297-332 (at 315), 1989.
46. U.S. Department of Health, Education, and Welfare, Public Health Service, Office on Smoking and Health, "14. Constituents of Tobacco Smoke: Toxicity of Specific Smoke Components," Smoking and Health. A Report of the Surgeon General, DHEW Publication No. (PHS) 79-50066, Washington, D.C., U.S. Government Printing Office, 78-84 (at 80), 1979.
47. Reinhardt, C.F. and Brittelli, M.R., "Chapter Thirty-Eight. Heterocyclic and Miscellaneous Nitrogen Compounds. 3.2.3. Dimethylnitrosamine." In: Patty's Industrial Hygiene and Toxicology. Third Revised Edition. G.D. Clayton and F. E. Clayton (eds.). New York, John Wiley & Sons, 2286-2789 (at 2786), 1982.

48. Huber, G.L., "Physical, Chemical, and Biologic Properties of Tobacco, Cigarette Smoke, and Other Tobacco Products," Seminars in Respiratory Medicine 10(4): 297-332 (at 311), October, 1989.
49. U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health, "Part III. Mechanisms of Carcinogenesis: Experimental Carcinogenesis With Tobacco Smoke," The Health Consequences of Smoking: Cancer. A Report of the Surgeon General: 1982, DHHS Publication No. (PHS) 82-50179, Washington, D.C., U.S. Government Printing Office, 181-235 (at 200), 1982.
50. Reinhardt, C.F. and Brittelli, M.R., "Chapter Thirty-Eight. Heterocyclic and Miscellaneous Nitrogen Compounds. 3.2.3. Dimethylnitrosamine." In: Patty's Industrial Hygiene and Toxicology. Third Revised Edition. G.D. Clayton and F. E. Clayton (eds.). New York, John Wiley & Sons, 2286-2789, 1982.
51. Fishbein, L., "Overview of Some Aspects of Occurrence, Formation and Analysis of Nitrosamines," Science of the Total Environment 13(2): 157-188, 1979.
- Pensabene, J., Fiddler, W., Doerr, R.C., Lakritz, L. and Wasserman, A.E., "Formation of Dimethylnitrosamine From Commercial Lecithin and its Components in a Model System," Journal of Agricultural and Food Chemistry 23(5): 979-980, 1975.
- Sen, N.P., Smith, D.C., Schwinghamer, L. and Marleau, J.J., "Food Additives: Dimethylnitrosamine and Other N-Nitrosamines in Foods," Journal of the Association of Official Analytical Chemists 52(1): 47-52, 1969.
52. Deichmann, W.B. and Keplinger, M.L., "Chapter Thirty-Six. Phenols and Phenolic Compounds. 1. Phenol." In: Patty's Industrial Hygiene and Toxicology. Third Revised Edition. G.D. Clayton and F.E. Clayton (eds.). New York, John Wiley & Sons, 2567-2584, 1982.
- Babich, H. and Davis, D.L., "Phenol: A Review of Environmental and Health Risks," Regulatory Toxicology and Pharmacology 1(1): 90-109 (see particularly 90, 103), 1981.
53. Deichmann, W.B. and Keplinger, M.L., "Chapter Thirty-Six. Phenols and Phenolic Compounds. 1. Phenol." In: Patty's Industrial Hygiene and Toxicology. Third Revised Edition. G.D. Clayton and F.E. Clayton (eds.). New York, John Wiley & Sons, 2567-2584 (at 2583-2584), 1982.
54. Kensler, C.J., Battista, S.P. and Thayer, P.S., "19. Animal Models for the Study of Tobacco Carcinogenesis." In: Human

Epidemiology and Animal Laboratory Correlations in Chemical Carcinogenesis. Frederick Coulston and Philippe Shubik (eds.). Norwood, New Jersey, Ablex Publishing Corporation, 341-357 (see particularly 351), 1980.

55. U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health, "Part III. Mechanisms of Carcinogenesis: Experimental Carcinogenesis With Tobacco Smoke," The Health Consequences of Smoking: Cancer. A Report of the Surgeon General: 1982, DHHS Publication No. (PHS) 82-50179, Washington, D.C., U.S. Government Printing Office, 181-235 (see particularly 190, 210), 1982.

U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health, "Section 3. Cancer," The Health Consequences of Smoking: The Changing Cigarette. A Report of the Surgeon General, DHHS Publication No. (PHS) 81-50156, Washington, D.C., U.S. Government Printing Office, 75-109 (see particularly 94), 1981.

56. Robertson, G.B. and Rogers, A.W., "An Autoradiographic Search for Radioactive Particles in the Lungs of Cigarette Smokers," Archives of Environmental Health 35(2): 117-122, March/April, 1980.

57. Cohen, B.S., Eisenbud, M. and Harley, N.H., "Measurement of the Alpha-Radioactivity on the Mucosal Surface of the Human Bronchial Tree," Health Physics 39(4): 619-632, 1980.

Harley, N.H., Cohen, B.S. and Tso, T.C., "Polonium-210: A Questionable Risk Factor in Smoking-Related Carcinogenesis." In: Banbury Report 3: A Safe Cigarette? G.B. Gori and F.G. Bock (eds.). Cold Spring Harbor, New York, Cold Spring Harbor Laboratory, 93-104, 1980.

58. Sandmeyer, E.E., "Chapter Forty-Seven. Aromatic Hydrocarbons. 1.3. Toluene." In: Patty's Industrial Hygiene and Toxicology. Third Revised Edition. G.D. Clayton and F. E. Clayton (eds.). New York, John Wiley & Sons, 3283-3291, 3400-3431, 1982.

59. Gibson, J.E. and Hardisty, J.F., "Chronic Toxicity and Oncogenicity Bioassay of Inhaled Toluene In Fischer-344 Rats," Fundamental and Applied Toxicology 3: 315-319, July/August, 1983.

Häsänen, E., Karlsson, V., Leppämäki, E. and Juhala, M., "Short Communication: Benzene, Toluene and Xylene Concentrations in Car Exhausts and in City Air," Atmospheric Environment 15(9): 1755-1757, 1981.

- Carpenter, C.P., Geary, D.L. Jr., Myers, R.C., Nachreiner, D.J., Sullivan, L.J. and King, J.M., "Petroleum Hydrocarbon Toxicity Studies. XIII. Animal and Human Response to Vapors of Toluene Concentrate," Toxicology and Applied Pharmacology 36(3): 473-490, 1976.
60. Canas, B.J., Havery, D.C., Robinson, L.R., Sullivan, M.P., Joe, F.L., and Diachenko, G.W., "Ethyl Carbamate Levels in Selected Fermented Foods and Beverages," Journal of the Association of Official Analytical Chemists 72(6): 873-876, 1989.
- Ingledew, W.M., Magnus, C.A., and Patterson J.R., "Yeast Foods and Ethyl Carbamate Formation in Wine," American Journal of Enology Viticulture 38(4): 332-335, 1987.
- Mossoba, M.M., Chen, J.T., Brumley, W.C., and Page, S.W., "Application of Gas Chromatography/Matrix Isolation/Fourier Transform Infrared Spectrometry to the Determination of Ethyl Carbamate in Alcoholic Beverages and Foods," Analytical Chemistry 60(9): 945-948, May 1, 1988.
61. U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health, "Part III. Mechanisms of Carcinogenesis: Experimental Carcinogenesis With Tobacco Smoke," The Health Consequences of Smoking: Cancer. A Report of the Surgeon General: 1982, DHHS Publication No. (PHS) 82-50179, Washington, D.C., U.S. Government Printing Office, 181-235 (see particularly 194), 1982.
62. Squirrell, D.C.M. and Thain, W., "Method 8 -- Determination of Vinyl Chloride in Foodstuffs by Head-Space Sampling Gas Chromatography." In: Environmental Carcinogens Selected Methods of Analysis. Volume 2 - Methods for the Measurement of Vinyl Chloride in Poly (Vinyl Chloride), Air, Water and Foodstuffs. H. Egan and W. Davis (eds.). Lyon, International Agency for Research on Cancer, IARC Scientific Publications, Monograph No. 22, 113-120 (see particularly p. 113), 1978.
- Albanus A.L., Gawell, B.-M., Larsson, B. and Slorach, S.A., "Sänkt maximigräns för vinylklorid i livsmedel (Reduced Maximum Tolerance for Vinyl Chloride in Foods)," Var Föda 31(3): 161-168, March, 1979. English Summary.
63. Torkelson, T.R. and V.K. Rowe, "Chapter Forty-Eight. Halogenated Aliphatic Hydrocarbons. 3. Unsaturated Halogenated Hydrocarbons. 3.1. Vinyl Chloride." In: Patty's Industrial Hygiene and Toxicology. Third Revised Edition. G.D. Clayton and F.E. Clayton (eds.). New York, John Wiley & Sons, 3537-3542, 3595-3596 (see particularly 3537), 1982.

64. Hoffmann, D., Patrianakos, C. and Brunnemann, K.D., "Chromatographic Determination of Vinyl Chloride in Tobacco Smoke," Analytical Chemistry 48(1): 47-50 (at 50), January, 1976.
65. Huber, G.L, "Physical, Chemical, and Biologic Properties of Tobacco, Cigarette Smoke, and Other Tobacco Products," Seminars in Respiratory Medicine 10(4): 297-332 (at 316), October, 1989.

CONSTITUENTS:

CLAIMS/RESPONSES

CLAIM: Tobacco smoke constituent levels should be printed on tobacco packs and in advertisements, or otherwise published, to protect the consumer.

RESPONSE: Such labeling would suggest that tobacco smoke constituents have been shown to be harmful. However, it has frequently been pointed out that although tobacco smoke constituents may be among the most heavily researched substances in the world, no constituent, as found in cigarette smoke, has been scientifically proven to cause cancer or any other human disease.¹ Even anti-smoking reports have conceded this.²

Reported constituent levels may be of limited value since the laboratory machines used to measure smoke constituents cannot duplicate the way humans smoke -- no two smokers smoke the same way and no smoker smokes the same way all the time. These testing difficulties have been acknowledged by the U.S. government.³

Constituent information may also be counterproductive from the point of view of those who argue that smoking is harmful. They would claim that these data help consumers

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switch to lower yield brands. However, in Sweden, young people reportedly used this information to select the "strongest" brands, i.e., those with the highest yields.⁴

REFERENCES

1. Okun, R., Statement, Re: "Cigarette Smoking and Disease, 1976." In: Hearings before the Committee on Labor and Public Welfare, Subcommittee on Health, United States Senate, Ninety-Fourth Congress, Second Session, 152-167, February 19, March 24, and May 27, 1976.

Schrauzer, G.N., Statement, Re: "Comprehensive Smoking Prevention Education Act." In: Appendix to Hearings before the Committee on Energy and Commerce, Subcommittee on Health and the Environment, United States House, Ninety-Seventh Congress, Second Session, 745-747, March 5, 11, and 12, 1982.

Seltzer, C.C., Statement, Re: "Comprehensive Smoking Prevention Education Act." In: Appendix to Hearings Before the House Committee on Energy and Commerce, Subcommittee on Health and the Environment, United States House, Ninety-Seventh Congress, Second Session, 748-757, March 5, 11, and 12, 1982.

2. U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health, "Part III. Mechanisms of Carcinogenesis," The Health Consequences of Smoking: Cancer. A Report of the Surgeon General: 1982, Washington, D.C., U.S. Government Printing Office, DHHS Publication No. (PHS) 82-50179, 171-235 (see particularly 218), 1982.

U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health, "Section 2. Arteriosclerosis," The Health Consequences of Smoking: Cardiovascular Disease. A Report of the Surgeon General: 1983, Washington, D.C., U.S. Government Printing Office, DHHS Publication No. (PHS) 84-50204, 2, 13-62 (see particularly 50, 51), 1983.

3. Gordon, R.T., "Barclay 1mg Claim Invalid, FTC Decides," Advertising Age, June 28, 1982.
4. Antoni F., Quoted in "He Warns Us of Smoking . . . and is a Heavy Smoker Himself," Hudikavallstidningen, Sweden, March 29, 1980.

CLAIM: Tobacco countries sell cigarettes in developing countries which have higher "tar" and nicotine yields than the same-brand cigarettes sold in western countries.

RESPONSE: This is not an accurate statement. Constituent levels of same-brand cigarettes generally are much the same wherever they are sold. A report of the evaluation of the "tar", nicotine and carbon monoxide yields of 50 brands of cigarettes available in 10 developing countries, issued by the World Health Organization, concluded that the constituent levels of cigarettes in those countries were very similar to those available in North America, Great Britain, and Europe.¹

In those cases where cigarettes are manufactured for export, manufacturers try to make the export product identical to the comparable brand sold in the country of origin for numerous reasons, including economies of scale which are such that it simply does not make sense to produce different versions of the same product for different markets. Manufacturers of cigarettes, like manufacturers of other products, also must insure that their customers get the same product worldwide or else run the risk of losing their loyalty and support.

Smokers, like any other consumer, want to be able to depend on consistent product quality.

There is a second category of product available in overseas markets, however, that may present a somewhat different situation. Those are international trademark brands which are made under license by local manufacturers. As the licensors, international manufacturers endeavor to have their brands made locally meet the same standards as those made in the country of origin. Nevertheless, their ability to control local manufacturing standards is understandably less in such situations. There are a number of reasons for this, including local laws and regulations which limit the amount of imported tobacco that can be used in locally made cigarettes and local trade preferences. For example, in the Philippines, international cigarette brands are produced by local licensees and, because of local law, are required to include a high percentage of locally grown tobacco; the use of local leaf results in a slightly higher "tar" and nicotine content than comparable brands manufactured and sold in the country of origin.

On the other hand, in some instances, brands sold in export markets may actually contain less "tar" and

nicotine than locally made brands. For example, the highest "tar" levels for cigarettes made in the United States are around 16 milligrams (mg.), while in Japan, Seven Stars Filter, a popular local cigarette brand, has 19.3 mg., and in Hong Kong, Good Companion has 18.3 mg. In fact, the average "tar" and nicotine levels of the cigarettes available to foreign consumers have actually decreased in some cases when American cigarettes become available.²

International cigarette manufacturers comply fully with local requirements regarding "tar" and nicotine levels. These include countries that have established upper limits on the "tar" and nicotine deliveries of cigarettes sold, such as Saudi Arabia, and countries which require the manufacturer to indicate the "tar" and nicotine deliveries on the cigarette products. Hong Kong, for example, utilizes a system similar to the one used in Great Britain, which defines "ranges" of "tar" and requires cigarette manufacturers to designate the "range" in which a particular brand falls on the package.

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REFERENCES

1. Frecker, R.C. and Pischkitl, H., Constituents of Cigarettes From Developing Countries: Nicotine, Tar and Carbon Monoxide Values for 50 Brands Selected By The World Health Organization, Geneva, World Health Organization, WHO/SMO/84.4, 1-12, 1984.
2. Whitley, C.O., Statement, Re: "Tobacco Issues (Part 1)."
In: Hearings Before the Committee on Energy and Commerce, Subcommittee on Transportation and Hazardous Materials, One Hundred First Congress, First Session, United States House, pp. 628-644, July 25 and September 13, 1989.

CLAIM: There are cancer-causing agents in tobacco smoke and that must explain the association between smoking and cancer.

RESPONSE: Researchers have been trying for many years to determine whether constituents of tobacco smoke cause human disease. Because of such studies, tobacco and tobacco smoke constituents may be among the most heavily researched substances in the world. However, after years of intensive research, no constituent as found in cigarette smoke has been scientifically proven to cause cancer or any other human disease.¹

REFERENCES

1. Okun, R., Statement, Re: "Cigarette Smoking and Disease, 1976." In: Hearings Before the Committee on Labor and Public Welfare, Subcommittee on Health, United States Senate, Ninety-Fourth Congress, Second Session, pp. 152-167, February 19, March 24, and May 27, 1976.

Schrauzer, G.N., Statement, Re: "Comprehensive Smoking Prevention Education Act." In: Appendix to Hearings Before the Committee on Energy and Commerce, Subcommittee on Health and the Environment, United States House, Ninety-Seventh Congress, Second Session, 745-747, March 5, 11, and 12, 1982.

CLAIM: It is well-known that "tar" is harmful to the smoker.

RESPONSE: "Tar" is an artificially created laboratory product consisting of highly concentrated and physically altered cigarette smoke particulate matter which is collected either by passing cigarette smoke through a cold trap at extremely low temperatures or by using filters and a drying process. The substances as found in "tar" are not found in cigarette smoke. A United States government report on smoking and health acknowledges that such mechanical processes hardly duplicate the way humans smoke.¹

Apparently, concern about "tar" is largely due to early experiments which involved painting this artificially produced substance on the skin of laboratory animals. The scientific value of such experiments has, however, been questioned for numerous reasons, including the fact that the skin of test animals is much different from the human lung tissue and because the quantities of "tar" used were unrealistically high.²

It is misleading, therefore, to draw definitive conclusions about "tar" and human disease from animal skin painting experiments.

REFERENCES

1. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, "Harmful Constituents of Cigarette Smoke," The Health Consequences of Smoking. Reference Edition, HEW Publication No. (CDC) 78-8357, Washington, D.C., U.S. Government Printing Office, Chapter 12, 621-634 (at 625), 1976.
2. Macdonald, I., Statement, Re: "False and Misleading Advertising (Filter-Tip Cigarettes)." In: Hearings Before the Committee on Government Operations, Legal and Monetary Affairs Subcommittee, United States House, Eighty-Fifth Congress, First Session, 224-240, July 18, 19, 23, 24, 25, and 26, 1957.

Hockett, R.C., Statement, Re: "Comprehensive Smoking Prevention Education Act." In: Appendix to Hearings Before the Committee on Energy and Commerce, Subcommittee on Health and the Environment, United States House of Representatives, Ninety-Seventh Congress, Second Session, 627-635, March 5, 11 and 12, 1982.

CLAIM: One hears a lot about nicotine and carbon monoxide. They must be the dangerous elements in tobacco smoke.

RESPONSE: Such claims are not based on scientific fact.

Nicotine is rapidly eliminated from the body. Even the 1964 United States Surgeon General's Report conceded that nicotine "probably does not represent a significant health problem."¹ The 1983 United States Surgeon General's Report, which focused on cardiovascular disease, also conceded that "the evidence for and against a primary role for nicotine in the development or acceleration of atherosclerosis is not conclusive,"² Similarly, other scientists have described nicotine as having no known or cumulative effects on human health.³

People are exposed to carbon monoxide (CO) from various sources, such as automobile exhaust fumes and industrial emissions every day, regardless of whether or not they smoke. However, it is the CO in cigarettes which has received considerable attention in the scientific literature, usually in regard to cardiovascular disease. Despite this attention, however, the issue of what role, if any, the small amounts of CO in tobacco smoke may have in disease causation has not been determined. Even

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the 1983 U.S. Surgeon General's Report conceded that there is no consensus in the scientific literature regarding the role, if any, of CO and heart disease.⁴

REFERENCES

1. U.S. Department of Health, Education, and Welfare, Public Health Service, "Chapter 7. Pharmacology and Toxicology of Nicotine," Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service, Washington, D.C., U.S. Government Printing Office, Public Health Service Publication No. 1103, 67-76 (at 75), 1964.
2. U.S. Department of Health and Human Services, U.S. Public Health Service, Office on Smoking and Health, "Section 2. Arteriosclerosis," The Health Consequences of Smoking: Cardiovascular Disease. A Report of the Surgeon General: 1983, DHHS Publication No. (PHS) 84-50204, Washington, D.C., U.S. Government Printing Office, 13-62 (at 50), 1983.
3. Hine, C.H., Statement, Re: "Cigarette Smoking and Disease, 1976." In: Hearings Before the Committee on Labor and Public Welfare, Subcommittee on Health, United States Senate, Ninety-Fourth Congress, Second Session, 127-145, February 19, March 24, and May 27, 1976.

Hockett, R.C., Statement, Re: "Smoking Prevention Education Act." In: Hearings Before the Committee on Energy and Commerce, Subcommittee on Health and the Environment, United States House of Representatives, Ninety-Eighth Congress, First Session, pp. 841-851, March 9 and 17, 1983.
4. U.S. Department of Health and Human Services, U.S. Public Health Service, Office on Smoking and Health, "Section 2. Arteriosclerosis," The Health Consequences of Smoking: Cardiovascular Disease. A Report of the Surgeon General: 1983, DHHS Publication No. (PHS) 84-50204, Washington, D.C., U.S. Government Printing Office, 13-62 (see particularly 51), 1983.

CLAIM: There are many substances in cigarette smoke. Even if "tar," nicotine and carbon monoxide don't cause disease in smokers, one or more of those other substances most likely do.

RESPONSE: Probably because efforts to establish that "tar," nicotine and CO cause human disease have been unsuccessful, some anti-smoking advocates have attempted to shift public attention to other substances in cigarette smoke, like arsenic and hydrogen cyanide. While these and many other substances are reportedly present in tobacco smoke, such claims fail to point out that the vast majority of those substances, some of which have been identified in "tar," are present only in extremely small amounts. As is the case with "tar," nicotine and CO, these minute quantities of other substances, as found in cigarette smoke, have not been proven to cause cancer or any other human disease.

Furthermore, these claims fail to point out that these substances are also present in the air we breathe, the water we drink, and even the food we eat. That is because these substances are for the most part the natural by-products of combustion of any organic matter, including tobacco, or are found in any organic matter whether or

not it is burnt. For example, arsenic is a naturally occurring metal that is also present in rocks, water, and virtually all living organisms in very tiny concentrations. However, even the 1982 U.S. Surgeon General's Report noted that the view that inorganic arsenics cause lung cancer has not been widely accepted.¹

Likewise, hydrogen cyanide is also generated by the combustion of carbon materials in the air, for example, during home cooking. Moreover, it is used in a variety of industrial processes and is present in such food products as lima beans, soy beans and apricots. It has even been detected in certain wines.² A researcher who has examined the literature on this subject recently concluded that what effect the hydrogen cyanide in cigarette smoke has, if any, on humans remains to be determined.³

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REFERENCES

1. U.S. Department of Health and Human Services, "Part III. Mechanisms of Carcinogenesis," Public Health Service, Office on Smoking and Health, The Health Consequences of Smoking: Cancer. A Report of the Surgeon General: 1982, DHHS Publication No. (PHS) 82-50179, Washington, D.C., U.S. Government Printing Office, 171-235 (at 212), 1982.
2. Hartung, R., "Chapter Fifty-Eight: Cyanides and Nitriles. 2. Cyanides. 2.1. Hydrogen Cyanide." In: Patty's Industrial Hygiene and Toxicology. Third Revised Edition. G.D. Clayton and F.E. Clayton (eds.). New York, John Wiley & Sons, 4850-4853 (see particularly 4850), 1982.

Honig, D.H., Hockridge, M.E., Gould, R.M. and Rackis, J.J., "Determination of Cyanide in Soybeans and Soybean Products," Journal of Agricultural and Food Chemistry, 31(2): 272-275, 1983.

Misselhorn, K., and Adam, R., "On The Cyanide Contents in Stone-Fruit Products," Branntweinwirtschaft, 116(4): 45-50, 1976. English Abstract.

Askar, A. and Morad, M.M., "Lebensmittelvergiftung. 1. Toxine in natürlichen Lebensmitteln (Food Poisoning. 1. Toxins in Natural Foodstuffs)," Alimenta 19: 59-66, 1980. English summary.
3. Huber, G.L., "Physical, Chemical, and Biologic Properties of Tobacco, Cigarette Smoke, and Other Tobacco Products," Seminars in Respiratory Medicine 10(4): 297-332 (at 312), October, 1989.

CLAIM: There is benzene in cigarette smoke. When benzene was detected in Perrier water, it was withdrawn from grocery shelves. If benzene in Perrier water is harmful, then benzene in cigarette smoke must be harmful too.

RESPONSE: While it is true that benzene has been reported to be present in the vapor phase of cigarette smoke, the levels are said to be very small. Furthermore, although benzene has sometimes been suggested as a possible cause of leukemia, that disease has not been related to cigarette smoke in any consistent fashion in the various statistical studies that form the primary basis for criticism of smoking.¹ Even the U.S. Surgeon General has noted that "no dose-response relationship has been established between death rate from leukemia and number of cigarettes smoked."²

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REFERENCES

1. Huber, G.L., "Physical, Chemical, and Biologic Properties of Tobacco, Cigarette Smoke, and Other Tobacco Products," Seminars in Respiratory Medicine 10(4): 297-332 (see particularly 312), October, 1989.
2. U.S. Department of Health, Education, and Welfare, Public Health Service, Office on Smoking and Health, "Chapter 14. Constituents of Tobacco Smoke: Benzenes and Naphthalenes," Smoking and Health. A Report of the Surgeon General, DHEW Publication No. (PHS) 79-50066, Washington, D.C., U.S. Government Printing Office, 49, 51 (at 51), 1979.

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CLAIM: Cigarette advertising certainly seems to imply that the newer, "lighter" cigarette brands are safe for people to smoke.

RESPONSE: The tobacco companies make no such claim. Low "tar" and nicotine cigarettes are on the market in response to consumer demand, which has increased in recent years. That demand appears to have developed as a result of the attention those products have received in the media. It certainly is consistent with consumer preferences for other "lighter" products now on the market, such as low-calorie beers, sugar-free soft drinks, low fat foods, and the like. Because of those changes in consumer preferences, tobacco manufacturers have modified their production and shifted their emphasis in advertising.

BUERGER'S DISEASE

Thromboangiitis obliterans or Buerger's Disease is an inflammatory condition of the small and medium-sized blood vessels of the arms and legs, leading to an insufficient supply of blood to the tissues. One of the charges against cigarette smoking is that it causes Buerger's Disease. This claim is based, in part, on reports alleging that a high percentage of patients with the disease smoke cigarettes. Despite such claims, the cause of Buerger's Disease is not yet known.¹ Moreover, problems created by frequent misdiagnoses and questions raised by the incidence or occurrence rates and other suggested theories of causation indicate that the causal hypothesis concerning Buerger's Disease and smoking is unproven.

Misdiagnosis

True Buerger's Disease is rare, even among young males in whom it reportedly occurs most frequently,² and misdiagnosis is common. For example, an American researcher who reviewed 205 cases diagnosed as Buerger's Disease at one hospital between 1933 and 1963 concluded that only 33 (16%) had a clinical picture compatible with the criteria for the disease.³ One explanation for such a large number of misdiagnosed cases may be that there are many other conditions and diseases with symptoms similar to those seen in Buerger's Disease patients. These conditions and diseases, which

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include atherosclerosis (vascular blockage caused by cholesterol plaques), frostbite, gout, ergotism (poisoning from the misuse or accidental ingestion of ergot, a type of rye plant fungus used for medicinal purposes), arterial embolism, scleroderma (a skin disease), an immunological disease called periarteritis nodosa, and occupational trauma, are not generally associated with smoking in the literature. For example, atherosclerosis, one of the diseases that is often confused with Buerger's Disease, is associated with high cholesterol levels and risk factors such as hypertension and diabetes mellitus.⁴ Accordingly, studies which suggest a strong association between Buerger's Disease and smoking may be flawed because it is likely that they include a number of cases in their analyses that are not actually Buerger's Disease.

Incidence of Buerger's Disease

Claims are made that the incidence of Buerger's Disease has risen and is increasing concurrently with the prevalence of smoking. However, this assertion is not consistent with the observation of a professor of medicine that "when the total number of heavy smokers in the general population is considered, the actual number in whom thromboangiitis obliterans develops is exceedingly small."⁵ Furthermore, this claim is not substantiated by reports that the incidence of Buerger's Disease in women is extremely low,

even though their smoking rates have increased dramatically in more recent years. For example, a 1973 worldwide literature review of female patients covering a period of almost 50 years reportedly found only 22 cases with microscopic findings that were compatible with those specified for the diagnosis of Buerger's Disease. Of those 22 cases, only eight were considered to be "probable" Buerger's Disease while the remainder were classified either as "possible" or only "doubtful."⁶ Between 1973 and 1986, only four additional cases of the disease in women were reported in the English-speaking literature.⁷ In 1986, however, a much higher incidence of Buerger's Disease was noted by an American researcher, who reported that 11 percent (12 out of 109 cases) of the patients registered with the disease at the well-known Mayo Clinic in Rochester, Minnesota, between 1981 and 1985 were women.⁸ Although he speculated that the apparent rise in the incidence of the disease among U.S. women might be related to their increased use of tobacco, the incidence of the disease in these women has not risen at the same rate as their prevalence of smoking. Therefore, this does not appear to be a satisfactory explanation.

The true incidence of Buerger's Disease in the general population is difficult to determine for numerous reasons. These include the possibility that a history of smoking has been a significant source of diagnostic bias among members of the medical profession because of the assumption that a smoker who presents

with symptoms suggestive of Buerger's Disease is more likely to have the disease than some other disease or condition with the same or similar symptoms. For example, a patient who may actually have, for example, peripheral vascular disease may be more likely to be diagnosed with Buerger's Disease largely because that individual also happens to smoke. Another reason is that the incidence rates reported in the literature are subject to certain population biases arising from the fact that most cases diagnosed as Buerger's Disease are referred to the care of health-care providers specializing in vascular diseases. Since the occurrence of the disease among such individuals or among those with peripheral vascular disease is likely to be higher than in the general population, applying those rates to the general population will likely lead to an artificially high overall rate.

There may be still other factors affecting the number of Buerger's Disease cases reported that have little to do with the true incidence of the disease. This is suggested by the dramatic changes in the reported incidence of the disease in the United States since it was first fully described by Dr. Buerger in an article in a medical journal in 1908⁹ and discussed more completely in his monograph in 1924.¹⁰ Between 1925 and 1945, one American physician claimed to have seen over 1,400 cases of Buerger's Disease, all in smokers.¹¹ In later years, however, the number of reported cases dropped dramatically. The reason for this drop is

unclear, although it has been speculated that the "popularity" of the disease as a medical diagnosis declined, perhaps in part because of the medical profession's greater adherence to stricter diagnostic criteria.¹² For example, in one study at the well-known Mayo Clinic, in Rochester, Minnesota, the prevalence rate dropped from 104/100,000 registered patients in 1947 to 13/100,000 patients in 1986, even though the clinical and pathologic criteria for the diagnosis of the disease remained the same.¹³

Tobacco and Buerger's Disease

Tobacco use has been implicated in the literature as a major cause of Buerger's Disease because of its reported temporal relationship with the clinical course of the disease. That is, many have suggested that the disease will progress with the continuation of smoking and that it will not progress if tobacco use is discontinued. However, a number of researchers have reported this not to be the case. For example, in a study of Buerger's Disease in the United States Army during and after World War II, "no significant association" between smoking habits of the patients after diagnosis and subsequent amputation rates was reported.¹⁴ Three years later, it was noted that a "careful" study of smoking habits in 81 patients with Buerger's Disease attending a British clinic "failed to find any effect of smoking on the course of the disease."¹⁵ Similarly, in another case study of a woman with

Buerger's Disease in England, there was no progression of the disease during a period of some years, despite the fact that she continued to smoke.¹⁶ The physicians who reported her case stated that in their experience, "the disease continues in some well-established cases, despite the cessation of smoking and also goes into remission despite continuation of smoking."¹⁷ Furthermore, in a 1988 paper on their retrospective study of 328 patients with Buerger's Disease, two Japanese researchers, Ohta and Shionoya, commented:

[N]o progression of symptoms was observed in about one-half of the patients who continued smoking, and a few patients suffered from ischaemic ulcers even though they had abstained from tobacco.¹⁸

Other questions about the relationship between tobacco and Buerger's Disease also raise doubts about the causal hypothesis. For example, if tobacco causes Buerger's Disease, how does one explain the cases reported among nonsmokers, even in very young children?¹⁹ Furthermore, how does one explain the differences seen over time in the ratio of male to female smokers with the disease?²⁰ In 1936, the ratio of women to men smokers in the United States was estimated at 1:6 while the ratio of women to men with Buerger's Disease was estimated at 1:70 to 1:500. In 1950, the ratio of women to men smokers fell to 1:4, yet there was "no proportionate increase" in the incidence of the disease among women

smokers.²¹ This suggests factors other than smoking must be involved.

Finally, some have claimed that since cigarette smoking has been related to Buerger's Disease, other forms of tobacco probably also play a role in the disease. However, a 1974 report on the results of a 20-year study of 25,000 snuff users and/or tobacco chewers in the state of Tennessee, where the use of these products is common, concluded that there was "no relationship between the use of unsmoked tobacco per se and intermittent claudication."²² Intermittent claudication (pain in the foot or calf after exercise of the affected muscle) is one of the first symptoms noted by a patient with Buerger's Disease.²³

Based on such observations, two British physicians, who describe Buerger's Disease as "a disease of unknown aetiology," concluded that the association between cigarette smoking and the disease "is not as clear as has been suggested in the past."²⁴

Other Suspected Factors

Buerger's Disease is reportedly more common in the Orient, Eastern Europe and the Mediterranean than North America and, although "no explanation has ever been offered for this peculiar geographic distribution of disease,"²⁵ it suggests the possible

involvement of genetic differences or environmental factors. A genetic influence is also suggested by the cases observed in nonsmokers and by the occasional familial occurrence of the disease reported in the literature.

Furthermore, a number of other suspects have been suggested as a cause of Buerger's Disease. These include fungal infections, socioeconomic class and/or occupation²⁶ and internal immune disorders.²⁷

Conclusion

Despite claims regarding Buerger's Disease and the use of tobacco, the role of tobacco, if any, has not been determined. True Buerger's Disease is a relatively rare occurrence in relation to the world's population of smokers. Moreover, the issues of misdiagnosis, incidence rates, and other possible risk factors and reports that the disease progresses even after smoking is discontinued raise many questions about the hypothesis that tobacco causes Buerger's Disease.

REFERENCES

1. Mills, J.L., Taylor, L.M. and Porter, J.M., "Buerger's Disease in the Modern Era," American Journal of Surgery 154(1): 123-129, July, 1987.

Adar, R., Papa, M.Z., Halpern, Z., Mozes, M., Shoshan, S., Sofer, B., Zinger, H., Dayan, M. and Mozes, E., "Cellular Sensitivity to Collagen in Thromboangiitis Obliterans," The New England Journal of Medicine 308(19): 1113-1116, May 12, 1983.

Morris-Jones, W. and Jones, C.D.P., "Buerger's Disease in Women: A Report of a Case and a Review of the Literature," Angiology 24(11): 675-690, 1973.
2. Mills, J.L., Taylor, L.M. and Porter, J.M., "Buerger's Disease in the Modern Era," American Journal of Surgery 154(1): 123-129, July, 1987.
3. Herman, B.E., "Buerger's Syndrome," Angiology 26(10): 713-716, 1975.
4. Wessler, S., Ming, S.-C., Gurewich, V. and Freiman, D.G., "A Critical Evaluation of Thromboangiitis Obliterans: The Case Against Buerger's Disease," The New England Journal of Medicine 262(23): 1149-1160, June 9, 1960.
5. Juergens, J.L., "Chapter 16: Thromboangiitis Obliterans (Buerger's Disease, TAO)." In: Peripheral Vascular Diseases. J.L. Juergens, J.A. Spittell and J.F. Fairbairn, II (eds.). Philadelphia, W.B. Saunders Company, 469-491 (at 471), 1980.
6. Morris-Jones, W. and Jones, C.D.P., "Buerger's Disease in Women: A Report of a Case and a Review of the Literature," Angiology 24(11): 675-690 (at 683), 1973.
7. Lie, J.T., "Thromboangiitis Obliterans (Buerger's Disease) in Women," Medicine 65(6): 65-72, 1986.
8. Lie, J.T., "Thromboangiitis Obliterans (Buerger's Disease) in Women," Medicine 65(6): 65-72, 1986.
9. Buerger, L., "Thromboangiitis Obliterans: A Study of the Vascular Lesions Leading to Presenile Spontaneous Gangrene," American Journal of Medical Sciences 136: 567-580, 1908.

10. Buerger, L. In: The Circulatory Disturbances of the Extremities: Including Gangrene, Vasomotor, and Trophic Disorders. Philadelphia, W.B. Saunders Company, 1924.
 11. Silbert, S., "Etiology of Thromboangiitis Obliterans," Journal of the American Medical Association 129(1): 5-9, September 1, 1945.
 12. Lie, J.T., "Thromboangiitis Obliterans (Buerger's Disease) Revisited." In: Pathology Annual. P.P. Rosen and R.E. Fechner (eds.). Norwalk, Connecticut, Appleton & Lange, Part 2, Volume 23, 257-291, 1988.
 13. Lie, J.T., "The Rise and Fall and Reemergence of Buerger's Disease, Especially in Women," Laboratory Investigation 60(1): 53A, January, 1989.
 14. DeBakey, M.E. and Cohen, B.M. In: Buerger's Disease: A Follow-Up Study of World War II Army Cases. Charles C. Thomas (ed.). Springfield, Illinois, 1-143 (at 129), 1963.
 15. Craven, J.L. and Cotton, R.C., "Haematological Differences Between Thromboangiitis Obliterans and Atherosclerosis," British Journal of Surgery 54(10): 862-867 (at 866), October, 1967.
 16. Morris-Jones, W. and Jones, C.D.P., "Buerger's Disease in Women: A Report of a Case and a Review of the Literature," Angiology 24(11): 675-690, 1973.
 17. Morris-Jones, W. and Jones, C.D.P., "Buerger's Disease in Women: A Report of a Case and a Review of the Literature," Angiology 24(11): 675-690 (at 685), 1973.
 18. Ohta, T. and Shionoya, S., "Fate of the Ischaemic Limb in Buerger's Disease," British Journal of Surgery 75(3): 259-262 (at 261), March, 1988.
 19. Marandian, M.-H., Saboury-Deilami, M., Rakchan, M., Lessani, M., Behvad, A. and Grouhi, M., "Thromboangeite Obliterante et Gangrene Distale Chez Un Enfant De 5 Ans (Thromboangiitis Obliterans and Distal Gangrene in a Five-Year-Old Child)," Pediatric 40(8): 653-657, 1985. English Summary.
- Juergens, J.L., "Chapter 16: Thromboangiitis Obliterans (Buerger's Disease, TAO)." In: Peripheral Vascular Diseases. J.L. Juergens, J.A. Spittell and J.F. Fairbairn, II (eds.). Philadelphia, W.B. Saunders Company, 469-491, 1980.
- Stojanovic, V.K., Marcovic, A., Arsov, V., Bujanic, J. and

Lotina, S., "Clinical Course and Therapy of Buerger's Disease," Journal of Cardiovascular Surgery 14(1): 5-8, January-February, 1973.

20. Morris-Jones, W. and Jones, C.D.P., "Buerger's Disease in Women: A Report of a Case and a Review of the Literature," Angiology 24(11): 675-690, 1973.
21. Morris-Jones, W. and Jones, C.D.P., "Buerger's Disease in Women: A Report of a Case and a Review of the Literature," Angiology 24(11): 675-690 (at 685), 1973.
22. Smith, J.F., "The Use of Unsmoked Tobacco and Intermittent Claudication," Journal of the Tennessee Medical Association 67(11): 913-914 (at 914), November, 1974.
23. Juergens, J.L., "Chapter 16: Thromboangiitis Obliterans (Buerger's Disease, TAO)." In: Peripheral Vascular Diseases. J.L. Juergens, J.A. Spittell and J.F. Fairbairn, II (eds.). Philadelphia, W.B. Saunders Company, 469-491, 1980.
24. Morris-Jones, W. and Jones, C.D.P., "Buerger's Disease in Women: A Report of a Case and a Review of the Literature," Angiology 24(11): 675-690 (at 684), 1973.
25. Mills, J.L., Taylor, L.M. and Porter, J.M., "Buerger's Disease in the Modern Era," American Journal of Surgery 154(1): 123-129 (at 123), July, 1987.
26. Hill, G.L., Moeliono, J., Tumewu, F., Brataamadja, D. and Tohardi, A., "The Buerger Syndrome in Java: A Description of the Clinical Syndrome and Some Aspects of its Aetiology," British Journal of Surgery 60(8): 606-613, August, 1973.
27. Adar, R., Papa, M.Z., Halpern, Z., Mozes, M., Shoshan, S., Sofer, B., Zinger, H., Dayan, M. and Mozes, E., "Cellular Sensitivity to Collagen in Thromboangiitis Obliterans," The New England Journal of Medicine 308(19): 1113-1116, May 12, 1983.

BUERGER'S DISEASE

CLAIMS/RESPONSES

CLAIM: Some smokers have to have their legs amputated because of "smoker's leg."

RESPONSE: This is probably a reference to Buerger's Disease. Individuals who have this problem with the blood vessels in their arms or legs may have to have the limb amputated if it becomes so serious that they develop gangrene.

This claim apparently is made about cigarette smoking because it has been reported that a high percentage of patients who have the disease are smokers. However, the claim overlooks the fact that nonsmokers also develop this disease.¹ It also overlooks the many medical and scientific "unknowns" about this disease. For example, it is not even known for certain how many people who have been diagnosed with this disease actually have it. That's because it's a rare disease, and mistakes in diagnosis are quite common, in part because there are numerous other diseases with very similar symptoms. For example, an American researcher who reviewed 205 cases that had been diagnosed as Buerger's Disease at one hospital between 1933 and 1963 reported that only 33 of

the cases, or about 16%, met the clinical criteria for a true diagnosis of Buerger's Disease.² If physicians have such difficulty even determining if a person has the disease, how can anyone claim that it has been proven what causes it?

REFERENCES

1. Juergens, J.L., "Chapter 16: Thromboangiitis Obliterans (Buerger's Disease, TAO)." In: Peripheral Vascular Diseases. Philadelphia, W.B. Saunders Company, J.L. Juergens, J.A. Spittell and J.F. Fairbairn, II (eds.), 469-491, 1980.
2. Herman, B.E., "Buerger's Syndrome," Angiology 26(10): 713-716, 1975.

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CLAIM: Smoking must cause Buerger's Disease because the disease gets worse in those who keep on smoking and gets better in those who stop.

RESPONSE: This claim overlooks the fact that nonsmokers also develop the disease.¹ It also does not take into account studies which report contradictory findings.² For example, in one study of more than 300 Japanese patients with the disease, the symptoms reportedly did not progress in many of the patients who continued to smoke and actually did progress in a few patients who stopped.³

REFERENCES

1. Juergens, J.L., "Chapter 16: Thromboangiitis Obliterans (Buerger's Disease, TAO)." In: Peripheral Vascular Diseases. Philadelphia, W.B. Saunders Company, J.L. Juergens, J.A. Spittell and J.F. Fairbairn, II (eds.), 469-491, 1980.
2. DeBakey, M.E. and Cohen, B.M., Buerger's Disease: A Follow-Up Study of World War II Army Cases, Springfield, Illinois, Charles C. Thomas, 1-143, 1963.
3. Ohta, T. and Shionoya, S., "Fate of the Ischaemic Limb in Buerger's Disease," British Journal of Surgery 75(3): 259-262 (at 261), March, 1988.

SMOKING AND ADDICTION: EXECUTIVE SUMMARY

For hundreds of years, individuals have chosen to smoke or not to smoke, to continue or to quit, as a matter of personal preference and free choice. In more recent years, however, it has been suggested that smokers are unable to make free-will choices, particularly about whether to quit smoking, because they are "addicts." But cigarette smokers are not "addicts." They are normal, rational people who happen to enjoy smoking, an activity that is the target of a highly vocal group.

Proponents of the view that smoking is an addiction claim that pharmacological reports on nicotine demonstrate that smoking is not voluntary. However, this literature has an extremely narrow focus and does not fully consider the many complex and personal motivations for smoking. Furthermore, the question of whether smoking is voluntary is more than just a scientific question. It also involves the philosophical concept of "free will." In short, the pharmacological literature does not provide an adequate basis for understanding smoking behavior. However, it is clear from daily common sense observation that smokers make a free choice to smoke.

The use of addictive drugs produces several objective physiological effects that are not observed in cigarette smokers. Addictive drugs are intoxicating, which means that they are used

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to try to escape reality and are associated with a deterioration in psychological and behavioral functioning. Such drugs lead to physical dependence, as manifested by a medically serious, potentially life-threatening withdrawal syndrome that develops during abstinence from the drug. Addiction also leads to tolerance, a need for progressively greater levels of the drug.

Because of the physiological aspects of addictive drugs, the motivations for their use fluctuate between the desire to become intoxicated and the need to avoid or reduce the adverse physical symptoms of withdrawal. Due to this continuous cycle of intoxication and withdrawal, a drug addict is unable to make rational decisions affecting his life in general, much less specifically whether to continue or quit drug use. By contrast, smokers do not become intoxicated. Neither has physical dependence been demonstrated to occur in smokers. Smokers' ability to think rationally is never compromised by smoking. They are always able to make reasoned choices about smoking and other aspects of their lives.

In an effort to label smoking an addiction, some antismoking organizations and researchers have attempted to broaden the definition of addiction. For example, recent reports on smoking behavior released by the United States and Canadian governments do not include physical dependence as a requirement for addiction.

However, removing objective physical effects from the definition constitutes a step backward in terms of understanding drug addiction, because it relegates addiction to little more than a description of any frequently occurring behavior. Thus, the word addiction is now sometimes used to describe running or jogging, watching television, sexual activity, even shopping and playing video games.

The literature indicates that although smoking may be a strong habit, it has not been demonstrated to be an addiction to nicotine. For example, chewing gum which contains nicotine does not substitute for the pleasure of cigarette smoking. Moreover, smokers can quit when they decide to do so. Almost everyone knows someone who has quit smoking. In fact, in the United States alone, government figures indicate that nearly half of all living adults who ever smoked have quit.

Claims have been made that cigarette smoking serves as a "gateway drug" to the use of "hard" drugs. This very questionable claim apparently stems from occasional reports that a chronological order may exist between smoking and illicit drug use. However, any possible association between cigarette smoking and the use of drugs is small and tenuous, if it exists at all. In addition, it is illogical to suggest that two activities are causally related just because one activity may precede the other.

In attempting to build credibility for a cigarette addiction claim, antismoking groups sometimes argue that this is the conclusion of the American Psychiatric Association. Although this organization does publish a diagnostic manual which includes categories for "dependence" and "withdrawal" in smokers, their inclusion may have been influenced by a variety of political, social and financial considerations not related to science. Moreover, the criteria for diagnosis of "dependence" have been criticized as overinclusive. The manual itself concedes that it is not known whether its diagnosis of "withdrawal" has anything to do with quitting smoking.

In conclusion, there have been increasingly frequent attacks on smoking, marked by attempts to label it an addiction. Lacking scientific demonstration of physiological criteria for addiction, these attacks have taken on a distinctly emotional and political tone. In fact, the "addiction" label appears to be applied to smoking with little regard for its scientific meaning. Cigarette smoking is more accurately classified as a habit. As when giving up any habit, a smoker needs the desire and the motivation to quit. There is nothing in cigarettes which interferes with a smoker's ability to decide to quit and to carry out that decision. In fact, in the United States alone, government figures indicate that over 41 million people, nearly half of all

living adults who ever smoked, have quit. Moreover, more than 90 percent of those have successfully quit on their own and without professional help.

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SMOKING AND ADDICTION

Tobacco smoking has been a popular custom for hundreds of years. Individuals have chosen to smoke or not to smoke, to continue or to quit, as a matter of personal preference and free choice. In more recent years, however, antismoking attacks have suggested that smokers are unable to make free-will choices, particularly about whether to quit smoking. Indeed, anti-smokers contend that cigarette smokers are "addicts." Cigarette smokers are not "addicts." They are normal, rational people who happen to enjoy smoking, an activity that is the target of a highly vocal group.

It seems that by calling smokers addicts, antismokers hope to eventually eliminate smoking as a social custom. Indeed, the social and political underpinning of the addiction claim was admitted by Dr. Morris A. Lipton, one of several scientists who was involved in developing the United States government's official position on smoking and addiction in the early 1980s. He gave the following reason for the government's use of the addiction label: "It was selected because it's sort of a dirty word."¹ Thus, it should be readily apparent that the term addiction was intended to have an emotional impact, and that it has been applied to smoking with little regard for its scientific meaning.

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Smoking is a Voluntary Activity

Those who claim smoking is an addiction obviously hope to imply that it is an involuntary act on the part of smokers--that they are compelled to smoke. But everyday observations make it clear that decisions about smoking reflect freely-made personal choices. Simply put, people smoke because they want to and because they enjoy it. It may become a habit, but they are not compelled to continue. Whether an individual continues to smoke or quits is a voluntary decision that each smoker makes. As noted by a staff member of the United Kingdom's Office on Population Censuses and Surveys, decisions to quit or continue smoking reflect "a rational and reasoned choice that smokers make and periodically renew."²

Proponents of the view that smoking is an addiction rely strongly on pharmacological reports to support their claim that smokers do not have this choice. There are two broad reasons why this literature does not provide a valid basis for such a claim. First, this literature has an extremely narrow focus and does not fully consider the many complex and personal motivations for smoking. Second, the question of whether smoking is a voluntary act is more than just a scientific question. It also involves the philosophical concept of "free will," a concept that is generally not addressed in the scientific literature on this subject.

The narrow nature of the pharmacological literature is reflected in its almost exclusive focus on nicotine. It does not adequately take into account the psychological and social functions that smoking may have. Nor does it properly recognize the importance of each smoker's decision-making processes. Perhaps the most well-known example of this approach is the 1988 United States Surgeon General's Report titled "Nicotine Addiction."³ As noted previously, even before its publication, the U.S. government had taken the position that smoking is an addiction in which nicotine has a pivotal role. That may have made the Report's characterization of smoking as an addiction to nicotine inevitable.

A similar emphasis on nicotine is seen in a 1989 Canadian report titled "Tobacco, Nicotine, and Addiction."⁴ This report was prepared under the auspices of the Royal Society of Canada and was an attempt to respond to the Canadian government's question of whether smoking should be labeled an addiction, a dependence, or a habit. The report concentrates on pharmacological literature and on nicotine in particular. It excludes serious discussion of complex psychological and social factors associated with smoking behavior. As with the 1988 U.S. Surgeon General's Report, the limited focus almost seemed to predetermine the Canadian report's conclusion that smoking is an addiction.

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The antismokers' emphasis on pharmacological literature is misplaced not simply because its narrowness excludes other potentially important factors involved in smokers' decisions about their habit. It also ignores the inherent inability of such reports either to prove or disprove the philosophical question of whether a behavior is voluntary. In this regard, both the American Medical Association (AMA) and the American Psychiatric Association (APA) have raised questions about whether a scientific basis exists for opinions regarding volition in general, not to mention a specific individual's volition. As stated by the AMA: "[F]ree will is an article of faith, rather than a concept that can be explained in medical terms. . . ."5 Similarly, the APA stated: "The concept of volition is the subject of some disagreement among psychiatrists."6

In the final analysis, the antismokers' claim that so-called addiction to smoking makes a person unable to control his behavior is little more than a philosophical position. It conveniently fits into the antismokers' agenda to ostracize tobacco products and their users. However, this claim is not only unsubstantiated by, and largely unrelated to, pharmacological literature, but it is clearly at odds with the daily common sense observation that smokers make a free choice to smoke.

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Smoking Does Not Fit The Scientific Meaning of Addiction

The word "addiction," often used interchangeably with "dependence," is a scientific term that generally refers to objective physiological effects of drugs -- namely intoxication, physical dependence, withdrawal, and tolerance. Intoxication means that when an addict uses drugs, he is trying to escape reality. His psychological and behavioral functioning deteriorates. Physical dependence means that an addict experiences an agonizing, potentially life-threatening, withdrawal syndrome when he has not obtained his accustomed "fix." Tolerance means that an addict's body needs ever greater levels of drug intake to regain the intoxicating "high" which is so important in his life. Besides their medical implications, all of these physical effects in turn lead to a progressive decrease in the addict's ability to function, on both an individual and societal level.

It is an inherent quality of addictive drugs that the motivations for their use fluctuate between the desire for a state of intoxication and the need to avoid or reduce the adverse physical symptoms of withdrawal. Regardless of where an addict is in this continuous cycle of intoxication and withdrawal, his ability to reason and to judge is impaired. Thus, he is unable to make rational decisions affecting his life in general, much less about whether to continue or quit his drug use.

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Does the cigarette smoker fit this picture? Of course not. Smokers do not seek to get "high." Their ability to think rationally is never compromised by smoking. They make reasoned choices about smoking and other aspects of their lives. Thus, they cannot be considered addicted or dependent in any sense comparable to true addictions, such as those involving heroin or cocaine. As an analysis by the German federal government concludes: "No major dependence, in the sense of addiction, has been proven to be caused by the consumption of tobacco products."⁷ In short, although cigarette smoking may be a habit for many smokers, it does not fall within the scientific meaning of addiction.

The dramatic physical, psychological and societal effects of drug addiction are in sharp contrast with the simple pleasures of cigarette smoking. Despite this obvious fact, some researchers have attempted to broaden the definition of addiction so that it includes smoking. Unfortunately, this relegates addiction to little more than a description of any frequently occurring behavior. That seems to be why the word addiction is sometimes used to describe distance running or jogging, watching television, sexual activity, even shopping. In the United States, former Surgeon General C. Everett Koop also contributed to the misuse of the term when he said in 1982 that video games are "addicting."⁸

Attempts to dilute the meaning of the word addiction are also reflected in the increasing use of the term dependence. This term is not used in the sense of physical dependence, which specifies the precise and objective characteristics of withdrawal. Rather, it often seems to be applied to any repetitive behavior that may be important to a person and, hence, may be difficult to stop. Even as early as 1974, Reginald Smart of Canada's Addiction Research Foundation noted that terms such as addiction and dependence "cover too much and attempt to bring under single rubrics types of drug use that are extremely disparate."⁹ Similarly, Dr. David Warburton, of Britain's Reading University, observed: "We all are 'dependent' for our ordinary happiness, gratification, emotional well-being and general quality of life on a whole range of people and objects."¹⁰ In short, the terms "addiction" and "dependence" become almost scientifically meaningless when they are used merely as descriptions of any valued behavior or well-engrained habit.

Smoking Does Not Involve Physical Dependence or Tolerance

Physical dependence, as demonstrated by a medically serious withdrawal syndrome, has been a central feature of traditional views of addiction. Yet, it has not been demonstrated that cigarette smokers develop physical dependence. Although some

people describe unpleasant feelings when they quit smoking, these are very inconsistent, generally not long-lasting and mild. They appear to be quite similar to the sort of psychological feelings people often have when they stop doing any enjoyable activity. According to a 1984 review of the smoking cessation literature, any evidence for physical dependence on smoking is highly questionable. It concluded that "the weight of the evidence does not support a view that unpleasant physical and psychological effects necessarily follow abstinence from smoking." Many of the reported effects following smoking cessation were noted to be "highly idiosyncratic with little known about the causal mechanisms."¹¹

The inconclusive literature on physical dependence in smokers may be why this requirement is not part of the definitions of addiction in several governmental reports. Perhaps only by excluding physical dependence was it possible to call smoking an addiction. This appears to be the approach taken in the 1989 Royal Society of Canada report, which described addiction as "a strongly established pattern of behavior" but did not mention physical dependence in its definition.¹² Similarly, the 1988 U.S. Surgeon General's Report discussed addiction as a kind of substance use that "controls or strongly influences behavior."¹³ Thus, even though both reports label smoking an addiction, their definitions

emphasize vague behavioral factors that do not distinguish between mere habits and true addictions.

Removing physical dependence from the definition constitutes a step backward in terms of understanding drug addiction. In fact, doing so may be seen as an admission of defeat in the scientific debate concerning the nature of smoking behavior. It has not been scientifically established that physical dependence occurs in cigarette smoking. What is clear is that whatever minor effects smoking may have are in no way comparable to the physical disruption produced by demonstrably addictive drugs.

Neither have cigarette smokers been shown to develop tolerance in any meaningful sense. By contrast, in drug addiction, tolerance reliably occurs and is reflected in a progressive increase in the level of drug use, as the addict seeks to become intoxicated or "high." The existence of tolerance usually indicates that there have been underlying physical changes that make it necessary to take increasing amounts of the drug to obtain the same previously experienced effects.

Tolerance claims concerning smoking tend to be highly anecdotal. For example, it is often pointed out that beginning smokers take a while to get used to the habit. The implication is that this is somehow related to nicotine, but this is a misuse of

the concept of tolerance. All habits take time to become established. For example, some mild degree of "tolerance," or increasing levels of an activity, is characteristic of many behaviors. It has been observed, for example, that drug addictions are not "uniquely characterized" by tolerance, which is "in fact a very general feature of the family of habits."¹⁴

Furthermore, the typical pattern of smoking, which tends to remain at a fairly constant level throughout the smoker's life, argues against the applicability of tolerance. Fairly soon after choosing to smoke, it has been noted, smokers "rapidly arrive at their preferred number of cigarettes per day and this number remains stable for years."¹⁵ This is in contrast to heroin and cocaine addicts, who continue to increase their levels of drug intake.

1988 Surgeon General's Report

The pronouncement on "nicotine addiction" by the 1988 U.S. Surgeon General's Report¹⁶ received considerable press attention. This governmental report took an extreme position, labeling nicotine as an addictive substance similar to heroin or cocaine. However, the Report has been strongly criticized. In the United Kingdom, for example, Dr. Warburton argued that there are major differences between cigarette smoking and addictive drug use. He contended that the Surgeon General "ignored the

discrepancies in his enthusiasm to find criteria to compare nicotine use with heroin and cocaine use."¹⁷ After a detailed review of the Surgeon General's criteria, he suggested that the addiction claim was politically motivated.

Professor Albert Hirsch, head of the Department of Pulmonary Medicine at the University of Paris, had a similar reaction to the Report. Although Dr. Hirsch is a vocal critic of the tobacco industry, he noted that tobacco "cannot be compared to drugs, especially hard drugs like heroin or other narcotics." He characterized such comparisons as an attempt "to fight an evil with misstatements or distortions of the truth."¹⁸

Even within the United States, strong criticisms have been raised concerning the Surgeon General's addiction claim. In U.S. Congressional testimony concerning the Report, a noted clinical psychologist, Dr. Theodore Blau, described the nicotine addiction claim as "misleading and potentially harmful."¹⁹ Similarly, Dr. Stephen Raffle, a clinical psychiatrist at the University of California, San Francisco, said he considered the Surgeon General's Report to be "narrow and one-sided." He contended its conclusion was "inevitable" because it "does not contain a psychiatric, psychological or sociological perspective."²⁰

Smokers Can Quit Smoking When They Decide To Do So

Some antismokers have argued that reports which conclude that most smokers continue to smoke even though they say they want to quit indicate the extreme difficulty in cessation and, hence, support the addiction hypothesis. However, reports of smokers' desires to quit smoking may be misleading. Even Lynn T. Kozlowski, a Canadian scientist well-known for his antitobacco views, noted that "answers to questions on 'wanting to stop' and 'trying to stop' have regularly been used uncritically." He "encouraged caution in what is made of what smokers say about their wish to give up smoking and their attempts to do so" and advised that "both what smokers say about their smoking and what researchers make of these statements should be read skeptically."²¹

The same could be said for some literature on smoking behavior that has implied that quitting smoking is a nearly impossible task, at which only a few succeed. This forms the basis for the claim that the "drug" nicotine has taken over people's ability to choose whether or not to smoke. But this is not a credible position when one looks at the facts. After all, even the 1988 Surgeon General's Report noted that over 41 million people in the United States have quit smoking -- 90 percent of them on their own.²² In 1989, the Surgeon General made this point even

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more dramatically, noting that: "Nearly half of all living adults who ever smoked have quit."²³

Moreover, the effort involved in quitting smoking is often highly exaggerated. If and when a smoker decides to quit, he might at most experience reactions that are very similar to those psychological feelings he might have after giving up any well-liked habit, such as gum chewing or watching television. The ability of smokers to quit when they choose to do so has been recognized even by many of the more well-known opponents of smoking. For example, consider the following:

It may also be that, for the general public, the stories circulating about the agony of abstinence serve as a self fulfilling prophesy: smokers expect it to be painful and therefore it is. Many give up their attempts to break the habit at the first sign of discomfort, anticipating greater pain, which in reality is not forthcoming.²⁴

[I]t is quite apparent that most smokers can stop without formal help.²⁵

I deplore those who characterize quitting smoking as a tortured, almost impossible process. For many people, it is easy; for most it is somewhere between easy and difficult; and only for a minority is it really difficult.²⁶

Furthermore, much has been made of the alleged high relapse rates among quitters. However, studies of such rates have been almost exclusively based on "therapeutic" samples -- that is,

people who have had difficulty in quitting smoking. In the words of one researcher, a conclusion to the effect that cigarette smoking is a very difficult habit to break is "based largely on the results of numerous studies of single therapeutic interventions with populations of self-selected subjects who had actively sought help."²⁷ A more realistic picture of quitting is reflected in the behavior of the vast majority of smokers who quit on their own.

Nicotine Gum Does Not Substitute For Smoking

The inability of nicotine gum to provide a substitute for cigarettes also demonstrates that the motivations for smoking are much more complex than simply to obtain nicotine. A nicotine gum has been marketed for several years in some European countries, and more recently in North America. It is sold as a smoking cessation "aid" and is often used in research studies of smoking behavior.

If, as proponents of the addiction view maintain, people smoke cigarettes only to obtain nicotine, then nicotine gum should satisfy the desire for a cigarette. In fact, the gum should be interchangeable with smoking and should make quitting smoking a simple matter of switching from cigarettes to the gum. However, nicotine gum has not been shown to have these effects. For example, people who quit smoking sometimes express the feeling that they

have a desire or craving to smoke. If this so-called craving were for nicotine, then it would seem that nicotine gum should eliminate it. Yet, even researchers who believe smoking is an addiction to nicotine report that nicotine gum does not have this effect.²⁸ Also contrary to what proponents of the addiction view would predict, nicotine gum alone is of questionable usefulness as a smoking cessation aid. For example, when nicotine gum is given as a cessation aid in a general medical practice, its effect on cessation rates has been described as "either small or nonexistent."²⁹

Smoking Is Not a "Gateway" to Drug Use

In recent years, claims have been made that cigarette smoking serves as a "gateway drug" to the use of "hard" drugs. This is a very questionable claim, but it was vigorously put forward by a former director of the United States National Institute on Drug Abuse, Dr. William Pollin,³⁰ and more recently by former Surgeon General Koop in his 1988 report.³¹ United States government researchers continue to advance this view.³²

Although it has sometimes been reported that a chronological order may exist between smoking and illicit drug use, this cannot be considered to mean a cause-and-effect relationship. After all, even if a hard drug user first smoked

cigarettes, he also undoubtedly first did a large variety of other things, such as drink milk or soft drinks, eat ice cream, ride a bicycle and so on. The point should be obvious: Just because one activity chronologically precedes another does not mean that the activities are causally related.

It is also important to note that even studies claiming an association between smoking and hard drug use report that the relationship, if any, is quite small and of dubious predictive value. For example, Dr. John O'Donnell, a researcher writing in a United States government publication, noted:

Whatever the nature of the association, it is small, and would not suggest that cigarette use would be a useful predictor of later drug use.³³

A similar conclusion was reached in a study of U.S. adults which attempted to assess the relationship between use of marijuana, alcohol and tobacco. Evidence for this relationship was described as "tenuous."³⁴

DSM-III and DSM-III-R

Another technique sometimes used by antismoking groups in attempting to build credibility for a cigarette addiction claim is to argue that this is the conclusion of other authoritative

organizations. For example, the third edition of the Diagnostic and Statistical Manual (DSM-III) of the American Psychiatric Association (APA), published in 1980, is often cited for its inclusion of the terms "tobacco dependence" and "tobacco withdrawal."³⁵ DSM-III marks the first time smoking behavior appeared in the APA's diagnostic manual. Its inclusion may have been influenced by a variety of considerations not relating to science. In this regard, a noted United States psychologist, Dr. William T. McReynolds, stated that introducing new psychiatric diagnoses into DSM-III involved processes that are "social and political, not scientific, in nature."³⁶ Also, the potential influence of financial considerations may have been present because insurance reimbursement for the "treatment" of smokers would not be possible without tobacco's inclusion in DSM-III.

Moreover, DSM-III's criteria for "tobacco dependence" are arguably largely meaningless because they can be used to classify almost any smoker as "tobacco dependent." In one survey of the United States general population, 90 percent of the smokers were reported to fulfill the DSM-III criteria for "tobacco dependence." This research, reported by Dr. John Hughes, a researcher at the University of Vermont, was supported by the U.S. National Institute on Drug Abuse. Despite this support from a strongly antismoking organization, Dr. Hughes and his colleagues

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stated that their results suggest that the DSM-III criteria for "tobacco dependence" are "overinclusive."³⁷

Perhaps in an attempt to resolve some of the weaknesses in DSM-III, a revised manual known as DSM-III-R was published in 1987.³⁸ In DSM-III-R, the terms "tobacco dependence" and "tobacco withdrawal" were changed to "nicotine dependence" and "nicotine withdrawal." DSM-III-R also revised some of the diagnostic criteria related to smoking, but these new criteria, as in DSM-III, often pertain to amorphous behavioral or psychological factors, rather than the objective physiological consequences of true addictive drug use. For example, DSM-III-R lists psychological criteria such as "desire" to quit, or "time spent" in the activity. Although four of the nine criteria allude to physiological factors, the remaining five are psychological or behavioral. Since only three are required for the diagnosis of nicotine dependence, the physiological criteria may be irrelevant to diagnosing an individual smoker. Furthermore, with regard to one of the physiological criteria, DSM-III-R specifically excludes tobacco by noting that with smoking there is an "absence of a clinically significant nicotine intoxication syndrome."³⁹

The APA's inclusion of smoking-related "withdrawal" diagnoses in these manuals does not establish that physical dependence occurs in smokers. In fact, both DSM-III and DSM-III-R

clearly state that many of the critical scientific questions related to possible nicotine "withdrawal" remain unanswered. Both versions concede that it is not known whether a reaction observed in an exsmoker is really withdrawal or merely some psychological response. DSM-III-R comments, for example, that any so-called "withdrawal" could simply reflect frustration due to giving up a pleasurable habit, or the "loss of a reinforcer."⁴⁰

The dubious significance of the diagnosis of "nicotine withdrawal" is perhaps most strikingly clear in DSM-III-R's own admission that no one knows whether this diagnosis has anything to do with quitting smoking. It states that: "Whether severe Nicotine Withdrawal decreases the ability to stop smoking or remain abstinent from smoking is unknown."⁴¹

In short, the tobacco-related terminology introduced by the APA's diagnostic manuals is overbroad and unhelpful in providing an explanation for smoking behavior. The diagnostic criteria given in DSM-III and DSM-III-R do not tell us whether smoking is an addiction or whether it is simply a habit. Consequently, these manuals fail to further the scientific understanding of smoking behavior.

Conclusion

In recent years, there have been increasingly frequent attacks on smoking, marked by attempts to label it an addiction. Lacking scientific demonstration of physiological criteria for addiction, these attacks have taken on a distinctly emotional and political tone. In fact, the "addiction" label appears to have been applied to smoking with little regard for its scientific meaning. Cigarette smoking is more accurately classified as a habit. As is the case when any habit is given up, a smoker who decides to quit needs the motivation and desire to act on that decision. There is nothing in cigarettes which interferes with a smoker's ability to decide to quit and to carry out that decision. If that were not the case, how does one explain that in the United States alone, over 41 million people, nearly half of all living adults who ever smoked, have quit smoking, most of them without professional help?

REFERENCES

1. Christensen, R., "Cigarettes Addictive, Panel Says," The News and Observer, Raleigh, North Carolina, Wednesday, September 3, 1980, 1 and 5B (at 5B).
2. Marsh, A., "Smoking: Habit or Choice?" Population Trends 37: 14-20 (at 18), 1984.
3. U.S. Department of Health and Human Services, The Health Consequences of Smoking: Nicotine Addiction. A Report of the Surgeon General. Publication No. DHHS (CDC) 88-8406, Washington, D.C., U.S. Government Printing Office, 1988.
4. Royal Society of Canada, "Tobacco, Nicotine, and Addiction," A Committee Report Prepared at the Request of The Royal Society of Canada for The Health Protection Branch, Health and Welfare Canada, August 31, 1989.
5. Board of Trustees, Committee on Medicolegal Problems, American Medical Association, "Insanity Defense in Criminal Trials and Limitation of Psychiatric Testimony," Journal of the American Medical Association 251(22): 2967-2981 (at 2978), 1984.
6. Insanity Defense Work Group, "American Psychiatric Association Statement on the Insanity Defense," American Journal of Psychiatry 140(6): 681-690 (at 687), 1983.
7. "Public Advertising for Drug Abuse in the Federal Republic of Germany," Deutscher Bundestag - 10. 10/3759, Wahlperiode, August 27, 1985, 6 pp. Uncertified translation.
8. Mattiace, P., "Surgeon General Says Video Games May Harm Children," The Associated Press, November 9, 1982, A.M. cycle.
9. Smart, R.G., "Addiction, Dependency, Abuse, or Use: Which Are We Studying with Epidemiology?" In: Drug Use. Epidemiological and Sociological Approaches. E. Josephson and E.E. Carroll (eds.). Washington, D.C., Hemisphere Publishing Corporation, Chapter 2, 23-42 (at 32), 1974.
10. Warburton, D.M., "Addiction, Dependence and Habitual Substance Use," Bulletin of The British Psychological Society 38: 285-288 (at 287-288), 1985.
11. Murray, A.L. and Lawrence, P.S., "Sequelae to Smoking Cessation: A Review," Clinical Psychology Review 4(2): 143-157 (at 143), 1984.

12. Royal Society of Canada, "Tobacco, Nicotine, and Addiction," A Committee Report Prepared at the Request of The Royal Society of Canada for The Health Protection Branch, Health and Welfare Canada, (at v), August 31, 1989.
13. U.S. Department of Health and Human Services, The Health Consequences of Smoking: Nicotine Addiction. A Report of the Surgeon General. Publication No. DHHS (CDC) 88-8406, Washington, D.C., U.S. Government Printing Office, at 248, 1988.
14. Ashton, H. and Stepney, R., "The Development of Smoking Behaviour." In: Smoking: Psychology and Pharmacology. H. Ashton and R. Stepney (eds.). New York, Tavistock Publications, Chapter 3, 42-65 (at 49), 1982.
15. Warburton, D.M., "Is Nicotine Use an Addiction?" The Psychologist 4: 166-170 (at 168), 1989.
16. U.S. Department of Health and Human Services, The Health Consequences of Smoking: Nicotine Addiction. A Report of the Surgeon General. Publication No. DHHS (CDC) 88-8406, Washington, D.C., U.S. Government Printing Office, 1988.
17. Warburton, D.M., "Is Nicotine Use an Addiction?" The Psychologist 4: 166-170 (at 166), 1989.
18. Hirsch, A., Interview on French Radio Network, Europe 1, May 18, 1988.
19. Blau, T.H., Statement, Re: "Health Consequences of Smoking: Nicotine Addiction." In: Hearing Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, United States House of Representatives, One Hundredth Congress, Second Session, 319-332 (at 319), July 29, 1988.
20. Raffle, S.M., Statement, Re: "Health Consequences of Smoking: Nicotine Addiction." In: Hearing Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, United States House of Representatives, One Hundredth Congress, Second Session, 311-318 (at 314), July 29, 1988.
21. Kozlowski, L.T., Herman, C.P. and Frecker, R.C., "What Researchers Make of What Cigarette Smokers Say: Filtering Smokers' Hot Air," The Lancet I(8170): 699-700, March 29, 1980.
22. U.S. Department of Health and Human Services, The Health Consequences of Smoking: Nicotine Addiction. A Report of the Surgeon General. Publication No. DHHS (CDC) 88-8406, Washington, D.C., U.S. Government Printing Office, at 466,

1988.

23. U.S. Department of Health and Human Services, Reducing the Health Consequences of Smoking: 25 Years of Progress. A Report of the Surgeon General. Publication No. DHHS (CDC) 89-8411, Washington, D.C., U.S. Government Printing Office, at 11, 1989.
24. Pertschuk, M.J., Pomerleau, O.F., Adkins, D. and Hirsh, C., "Smoking Cessation: The Psychological Costs," Addictive Behaviors 4(4): 345-348 (at 347), 1979.
25. Jaffe, J.H. and Kanzler, M., "Smoking As An Addictive Disorder." In: Cigarette Smoking as a Dependence Process. N.A. Krasnegor (ed.). National Institute on Drug Abuse Research Monograph 23, Publication No. DHEW (ADM) 79-800, Washington, D.C., U.S. Government Printing Office, Chapter 2, 4-23 (at 16), 1979.
26. Horn, D., "Psychological Analysis of Establishment and Maintenance of the Smoking Habit." In: Cigarette Smoking as a Dependence Process. N.A. Krasnegor (ed.). National Institute on Drug Abuse Research Monograph 23, Publication No. DHEW (ADM) 79-800, Washington, D.C., U.S. Government Printing Office, Chapter 3, 24-29 (at 25), 1979.
27. Schachter, S., "Recidivism and Self-Cure of Smoking and Obesity," American Psychologist 37(4): 436-444 (at 436), 1982.
28. Hughes, J.R., Hatsukami, D.K., Pickens, R.W., Krahn, D., Malin, S. and Luknic, A., "Effect of Nicotine on the Tobacco Withdrawal Syndrome," Psychopharmacology 83(1): 82-87, 1984.

Hughes, J.R. and Hatsukami, D., "Short-Term Effects of Nicotine Gum." In: Pharmacological Adjuncts in Smoking Cessation. J. Grabowski and S.M. Hall (eds.). National Institute on Drug Abuse Research Monograph 53, Publication No. DHHS (ADM) 85-1333, Washington, D.C., U.S. Government Printing Office, 68-82, 1985.
29. Hughes, J.R., Gust, S.W., Keenan, R.M., Fenwick, J.W. and Healey, M.L., "Nicotine Vs Placebo Gum in General Medical Practice," Journal of the American Medical Association 261(9): 1300-1305 (at 1300), 1989.
30. Ravenholt, R.T. and Pollin, W., "Tobacco Addiction and Other Drug Abuse Among American Youth," manuscript for presentation to the 5th World Conference on Smoking and Health, Winnipeg, Canada, July 13, 1983.

31. U.S. Department of Health and Human Services, The Health Consequences of Smoking: Nicotine Addiction, A Report of the Surgeon General. Publication No. DHHS (CDC) 88-8406, Washington, D.C., U.S. Government Printing Office, 1988.
32. Henningfield, J.E., Clayton, R. and Pollin, W., "Involvement of Tobacco in Alcoholism and Illicit Drug Use," British Journal of Addiction 85(2): 279-292, 1990.
33. O'Donnell, J.A., "Cigarette Smoking as a Precursor of Illicit Drug Use." In: Cigarette Smoking as a Dependence Process. N.A. Krasnegor (ed.). National Institute on Drug Abuse Research Monograph 23, Publication No. DHEW (ADM) 79-800, Washington, D.C., U.S. Government Printing Office, Chapter 4, 30-43 (at 42), 1979.
34. Dull, R.T. and Williams, F.P., "Marihuana, Alcohol and Tobacco: Reassessment of a Presumed Relationship," Journal of Drug Education 11(2): 129-139 (at 135), 1981.
35. American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, (3rd ed.), Washington, D.C., American Psychiatric Association, 1980.
36. McReynolds, W.T., "DSM-III and the Future of Applied Social Science," Professional Psychology 10(1): 123-132 (at 125), 1979.
37. Hughes, J.R., Gust, S.W. and Pechacek, T.F., "Prevalence of Tobacco Dependence and Withdrawal," American Journal of Psychiatry 142(2): 205-208 (at 205), 1987.
38. American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, (3rd ed. - rev.), Washington, D.C., American Psychiatric Association, 1987.
39. American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, (3rd ed. - rev.), Washington, D.C., American Psychiatric Association, at 168, 1987.
40. American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, (3rd ed. - rev.), Washington, D.C., American Psychiatric Association, at 150, 1987.
41. American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, (3rd ed. - rev.), Washington, D.C., American Psychiatric Association, at 151, 1987.

ADDICTION:

CLAIMS/RESPONSES

CLAIM: Because of addiction to nicotine, smokers do not have voluntary control over their smoking.

RESPONSE:

- This claim is based on pharmacological reports. This literature, however, cannot explain smoking behavior, because it has an extremely narrow focus on a single constituent of cigarettes, namely nicotine. It does not fully consider the many complex and personal motivations for smoking.

- Cigarette smokers are always able to make rational choices about their lives in general and about whether to smoke in particular. A staff member of the United Kingdom's Office on Population Censuses and Surveys described decisions about whether to smoke as reflecting "a rational and reasoned choice that smokers make and periodically renew."¹ In contrast to cigarette smokers, drug addicts are unable to think rationally because of intoxication or withdrawal.

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-- Medical and psychiatric organizations recognize that the meaning of volition or voluntariness is unclear and cannot be explained in medical or scientific terms.²

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REFERENCES

1. Marsh, A., "Smoking: Habit or Choice?" Population Trends 37: 14-20 (at 18), 1984.
2. Board of Trustees, Committee on Medicolegal Problems, American Medical Association, "Insanity Defense in Criminal Trials and Limitation of Psychiatric Testimony," Journal of the American Medical Association 251(22): 2967-2981, 1984.

Insanity Defense Work Group, "American Psychiatric Association Statement on the Insanity Defense," American Journal of Psychiatry 140(6): 681-690, 1983.

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CLAIM: Cigarette smoking is addictive.

RESPONSE:

- The scientific definition of addiction generally includes objective physiological effects of drugs -- namely intoxication, physical dependence, withdrawal and tolerance. These effects are seen in heroin and cocaine addicts but not in cigarette smokers.
- Some recent definitions of addiction are so broad that they can apply to almost any strong habit. Watching television, exercising, and even shopping and playing video games have been called addictions. Broad definitions of addiction are meaningless because they include such a wide variety of activities.¹
- Because true drug addicts are usually either intoxicated or experiencing physical withdrawal, they are unable to make rational decisions concerning their lives in general, much less specifically whether to continue or quit drug use. By contrast, smokers are always able to think rationally. As noted by a staff member of the United Kingdom's Office on Population Censuses and Surveys, decisions to quit or continue smoking reflect "a

rational and reasoned choice that smokers make and
periodically renew."2

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REFERENCES

1. Smart, R.G., "Addiction, Dependency, Abuse, or Use: Which Are We Studying with Epidemiology?" In: Drug Use, Epidemiological and Sociological Approaches. E. Josephson and E.E. Carroll (eds.). Washington, D.C., Hemisphere Publishing Corporation, Chapter 2, pp. 23-42, 1974.

Warburton, D.M., "Addiction, Dependence and Habitual Substance Use," Bulletin of The British Psychological Society 38: 285-288, 1985.
2. Marsh, A., "Smoking: Habit or Choice?" Population Trends 37: 14-20 (at 18), 1984.

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CLAIM: Cigarette smoking is an addiction to nicotine similar to heroin and cocaine addiction.

RESPONSE:

- This claim was made by the 1988 U.S. Surgeon General's Report.¹ Although it received considerable press attention, it has been strongly criticized by scientists and clinicians from a number of countries.
- In the United Kingdom, Dr. David Warburton, of Reading University, noted that the U.S. Surgeon General ignored the discrepancies between cigarette smoking and addictive drug use. After a detailed review of the Surgeon General's position, he suggested that the addiction claim was politically motivated.²
- Professor Albert Hirsch, of the University of Paris, strongly disagreed with the U.S. Surgeon General's Report. He noted that tobacco "cannot be compared to drugs, especially hard drugs like heroin or other narcotics." He characterized such comparisons as an attempt "to fight an evil with misstatements or distortions of the truth."³

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-- Strong criticisms have been raised in U.S. Congressional testimony concerning the Surgeon General's addiction claim. A noted clinical psychologist described the nicotine addiction claim as "misleading and potentially harmful."⁴ A psychiatric expert testified that the Surgeon General's Report was "narrow and one-sided." Its conclusion was "inevitable," according to this witness, because it "does not contain a psychiatric, psychological or sociological perspective."⁵

REFERENCES

1. U.S. Department of Health and Human Services, The Health Consequences of Smoking: Nicotine Addiction. A Report of the Surgeon General. Publication No. DHHS (CDC) 88-8406, Washington, D.C., U.S. Government Printing Office, 1988.
2. Warburton, D.M., "Is Nicotine Use an Addiction?" The Psychologist 4: 166-170, 1989.
3. Hirsch, A., Interview on French Radio Network, Europe 1, May 18, 1988.
4. Blau, T.H., Statement, Re: "Health Consequences of Smoking: Nicotine Addiction." In: Hearing Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, United States House of Representatives, One Hundredth Congress, Second Session, 319-332 (at 319), July 29, 1988.
5. Raffle, S.M., Statement, Re: "Health Consequences of Smoking: Nicotine Addiction." In: Hearing Before the Subcommittee on Health and the Environment of the Committee on Energy and Commerce, United States House of Representatives, One Hundredth Congress, Second Session, 311-318 (at 314), July 29, 1988.

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CLAIM: Cigarette smokers develop physical dependence on nicotine, as reflected in a withdrawal syndrome which occurs when they try to stop smoking.

RESPONSE:

- Although some people describe unpleasant feelings when they quit smoking, these are very inconsistent, generally not long-lasting and mild. They appear to be quite similar to the sort of psychological feelings people often have when they stop doing any enjoyable activity. Whatever experiences some people have when they quit smoking appear to be "highly idiosyncratic."¹
- Physical dependence is not included as a requirement in some recent definitions of addiction. This, in itself, may reflect a recognition of the inconclusiveness of the literature on physical dependence in smokers. In other words, only by not including physical dependence as part of the definition could smoking be called an addiction. Unfortunately, this also means that no distinction is made between mere habits and true addictions.
- The inability of nicotine gum to provide a substitute for cigarettes also demonstrates that the desire to smoke

cannot stem simply from a physical dependence on nicotine. If people smoke because of a physical need for nicotine, then nicotine gum should satisfy the desire for a cigarette. In fact, the gum should make quitting smoking a simple matter of switching from cigarettes to the gum. Yet, even researchers who believe smoking is an addiction to nicotine report that nicotine gum does not have these effects.²

REFERENCES

1. Murray, A.L. and Lawrence, P.S., "Sequelae to Smoking Cessation: A Review," Clinical Psychology Review 4(2): 143-157 (at 143), 1984.
2. Hughes, J.R., Hatsukami, D.K., Pickens, R.W., Krahm, D., Malin, S. and Luknic, A., "Effect of Nicotine on the Tobacco Withdrawal Syndrome," Psychopharmacology 83 (1): 82-87, 1984.

Hughes, J.R. and Hatsukami, D., "Short-Term Effects of Nicotine Gum." In: Pharmacological Adjuncts in Smoking Cessation. J. Grabowski and S.M. Hall (eds.). National Institute on Drug Abuse Research Monograph 53, Publication No. DHHS (ADM) 85-1333, Washington, D.C., U.S. Government Printing Office, 68-82, 1985.

Hughes, J.R., Gust, S.W., Keenan, R.M., Fenwick, J.W. and Healey, M.L., "Nicotine Vs Placebo Gum in General Medical Practice," Journal of the American Medical Association 261(9): 1300-1305, 1989.

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CLAIM: Cigarette smokers develop tolerance to nicotine and smoking.

RESPONSE:

-- Most smokers develop a fairly level habit. For example, it has been observed that smokers "rapidly arrive at their preferred number of cigarettes per day and this number remains stable for years."¹ This is in contrast to heroin and cocaine addicts, who continue to increase their levels of drug intake.

-- Smokers take a while for the habit to become established. In this sense, "tolerance" is characteristic of many behaviors. That is, the development of any habit can be expected to have an initial period during which its frequency increases. It has been observed, for example, that drug addictions are not "uniquely characterized" by tolerance, which is "in fact a very general feature of the family of habits."²

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REFERENCES

1. Warburton, D.M., "Is Nicotine Use an Addiction?" The Psychologist 4: 166-170 (at 168), 1989.
2. Ashton, H. and Stepney, R., "The Development of Smoking Behaviour." In: Smoking: Psychology and Pharmacology. H. Ashton and R. Stepney (eds.). New York, Tavistock Publications, Chapter 3, 42-65 (at 49), 1982.

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CLAIM: Most cigarette smokers want to quit, but are unable to do so because of their addiction.

RESPONSE:

-- Reports of smokers' desires to quit smoking may be misleading. Some smokers may say they want to quit simply to please someone else, such as their spouse or employer. Yet, they may enjoy smoking and have no true motivation to stop. Accordingly, what smokers say about their desire and attempts to give up smoking should be viewed with a certain amount of skepticism.¹

-- Claims that quitting smoking is a nearly impossible task, at which only a few succeed, are not supported by the facts. After all, even the 1988 United States Surgeon General's Report noted that over 41 million people in that country have quit smoking -- 90 percent of them on their own.² In 1989, the Surgeon General made this point even more dramatically, noting that: "Nearly half of all living adults who ever smoked have quit."³

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REFERENCES

1. Kozlowski, L.T., Herman, C.P. and Frecker, R.C., "What Researchers Make of What Cigarette Smokers Say: Filtering Smokers' Hot Air," The Lancet I(8170): 699-700, 1980.
2. U.S. Department of Health and Human Services, The Health Consequences of Smoking: Nicotine Addiction. A Report of the Surgeon General. Publication No. DHHS (CDC) 88-8406, Washington, D.C., U.S. Government Printing Office, at 466, 1988.
3. U.S. Department of Health and Human Services, Reducing the Health Consequences of Smoking: 25 Years of Progress. A Report of the Surgeon General. Publication No. DHHS (CDC) 89-8411, Washington, D.C., U.S. Government Printing Office, at 11, 1989.

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CLAIM: Smoking is a "gateway" to the use of hard drugs.

RESPONSE:

- Even studies claiming an association between smoking and hard drug use report that the relationship, if any, is quite small and of dubious predictive value.¹

- Any reported chronological order between smoking and illicit drug use cannot be considered to mean a cause-and-effect relationship. After all, even if a hard drug user first smoked cigarettes, he also undoubtedly first did a large variety of other things, such as drink milk or soft drinks, eat ice cream, ride a bicycle and so on. The point should be obvious: Just because one activity chronologically precedes another does not mean that the activities are causally related.

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REFERENCES

1. O'Donnell, J.A., "Cigarette Smoking as Precursor of Illicit Drug Use." In: Cigarette Smoking as a Dependence Process. N.A. Krasnegor (ed.). National Institute on Drug Abuse Research Monograph 23, Publication No. DHEW (ADM) 79-800, Washington, D.C., U.S. Government Printing Office, Chapter 4, 30-43, 1979.

Dull, R.T. and Williams, F.P., "Marihuana, Alcohol and Tobacco: Reassessment of a Presumed Relationship," Journal of Drug Education 11(2): 129-139, 1981.

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CLAIM: Cigarette smoking is recognized as an addiction by the American Psychiatric Association.

RESPONSE:

- Recent American Psychiatric Association (APA) diagnostic manuals (known as DSM-III¹ and DSM-III-R²) have included diagnoses for "dependence" and "withdrawal" in smokers. However, their inclusion may have been influenced by a variety of social and political considerations.³ There may also have been a financial influence because the manuals are used as a basis for insurance reimbursement.
- DSM-III's criteria for "tobacco dependence" are arguably largely meaningless because they can be used to classify almost any smoker as "tobacco dependent." In one survey of the U.S. general population, 90 percent of the smokers were reported to fulfill the DSM-III criteria for "tobacco dependence." Based on these results, the government-supported researchers suggested that the DSM-III criteria for "tobacco dependence" are "overinclusive."⁴
- The APA's inclusion of a smoking-related "withdrawal" diagnosis does not establish that physical dependence occurs in smokers. DSM-III-R states, for example, that

any so-called "withdrawal" could simply reflect frustration due to giving up a pleasurable habit, or the "loss of a reinforcer."⁵

- The dubious significance of the diagnosis of "nicotine withdrawal" is perhaps most strikingly clear in DSM-III-R's own admission that no one knows whether this diagnosis has anything to do with quitting smoking. It states: "Whether severe Nicotine Withdrawal decreases the ability to stop smoking or remain abstinent from smoking is unknown."⁶

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REFERENCES

1. American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, (3rd ed.), Washington, D.C., American Psychiatric Association, 1980.
2. American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, (3rd ed. - rev.), Washington, D.C., American Psychiatric Association, 1987.
3. McReynolds, W.T., "DSM-III and the Future of Applied Social Science," Professional Psychology 10(1): 123-132, 1979.
4. Hughes, J.R., Gust, S.W. and Pechacek, T.F., "Prevalence of Tobacco Dependence and Withdrawal," American Journal of Psychiatry 142(2): 205-208 (at 205), 1987.
5. American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, (3rd ed. - rev.), Washington, D.C., American Psychiatric Association, at 150, 1987.
6. American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, (3rd ed. - rev.), Washington, D.C., American Psychiatric Association, at 151, 1987.

PESTICIDES

The use of pesticides in the growing and storing of tobacco may result in the detection of very small residual amounts of these substances in tobacco products. Claims have been made that these residues in cigarettes may play a role in the causation of certain diseases. However, no persuasive scientific studies have been reported which establish that the very small amounts of residues that have been detected in cigarette smoke cause disease in smokers.¹⁻³ Furthermore, extensive government regulation of pesticide use is designed to assure their proper use and application in the growth and cultivation of tobacco.

Pesticides are important agricultural chemicals that are widely used in the production of farm crops throughout the world. The term "pesticide" refers to those chemicals that are formulated and marketed by chemical manufacturers to control a wide range of pests that can cause substantial agricultural production losses. These include insects (insecticides), weeds (herbicides), worms (nematocides), fungi (fungicides), rodents (rodenticides) and other organisms. Accordingly, pesticides make an important contribution to worldwide agricultural success. As a result of approved uses, small amounts of residues from these chemicals are found in virtually all the foods in one's daily diet. Pesticides used in

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growing these food commodities are also used in tobacco agriculture.

Pesticides in Perspective

In order to understand the significance of the small amounts of pesticides reportedly found on agricultural crops, it is important to place pesticides and their residue levels in the proper perspective. A pesticide should not be perceived as a health risk simply because it is synthetic or man-made and has been used in agriculture. The mechanism of action that makes pesticides effective in controlling various pests and weeds does not automatically translate into health concerns or an adverse impact on the environment.

To evaluate the possible effect of small residues of pesticides, one must also consider other sources of chemicals that contribute to the array of substances to which humans are exposed. Even though synthetic pesticides are used all over the world, the major source of pest control chemicals is nature itself. All grain, fruit and vegetable plants are known to produce "pesticides" as chemical defenses to infestation by insects, fungi and animal predators. It has been estimated, for example, that one's diet includes about 1.5 grams of these natural "pesticides" during an average day, an amount which has been calculated to be about 10,000

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times the amount of synthetic pesticide residues consumed. In other words, 99.99% of the pesticides consumed through the diet are naturally-occurring.⁴

Pesticide Residues on Tobacco

In evaluating the claims about pesticide residues in tobacco, as with the potential hazards associated with exposure to any substance, it is necessary to consider the fundamental toxicological concept that "the poison is in the dose."^{5,6} Any substance given at a high enough dose is toxic, even oxygen and water. Likewise, any substance given at a dose well below its level of demonstrated toxicity would not be expected to result in toxic effects. The applicability of this concept in evaluating any potential effect of human exposure to the extremely low levels of pesticide residues that may be detectable in tobacco is readily apparent.

Tobacco undergoes substantial transformation from the raw leaf to the manufactured cigarette. The levels of pesticide residues that may be found on raw tobacco at the time of harvest are greatly reduced by the time the tobacco is incorporated into the final product. This transformation from the raw leaf to the cigarette is a result of the curing, aging, blending and manufacturing processes employed to produce a finished product

acceptable to the consumer. A significant reduction of pesticide residues occurs during curing, aging and blending. Moreover, steam and heat used in the manufacturing process lead to substantial reductions in residue levels. All of these processing steps and the necessary time lapse that occurs, from harvest of the raw tobacco to the final manufactured product, result in extensive dissipation of the residues.

Even the tiny amounts of pesticide residues that may be present in the final cigarette do not represent the amounts, if any, that may ultimately transfer into mainstream smoke. (Mainstream smoke is the smoke that is drawn through the rod of a burning cigarette by the smoker.) For example, residues of maleic hydrazide that may be detectable in cigarettes do not appreciably transfer into mainstream smoke; a mainstream transfer rate of approximately 0.2% has been reported.⁷ Not even the United States Surgeon General has claimed that the pesticide residues detectable in cigarettes are a proven health problem.^{8,9}

Government Regulation

In many countries, the use of pesticides and the presence of residues in agricultural food commodities are subject to government regulation. These countries have developed pesticide approval standards, based on extensive scientific data, for the

purpose of ensuring that the regulated pesticide residues do not represent a risk to environment or health. The purpose of such government regulations is to ensure the proper use of approved pesticides to enhance crop production without exposing the farmer, the consumer or the environment to risk. It is the practice of the major tobacco manufacturers to purchase and use only that tobacco grown and sold in accordance with the government regulations applicable in the respective countries.

The extent to which governments regulate pesticides varies from country to country. For example, among the European countries, Germany is noted to have a comprehensive set of pesticide tolerances on tobacco and other crops. Many of its neighbors refer to Germany's regulations to govern pesticide tolerance levels in their own countries. The German regulations specify maximum permitted levels on tobacco for residues of many pesticides; the use of other specified pesticides is also allowed if prescribed agricultural practices are followed and the residues do not exceed a recommended maximum amount. These residue levels are applicable to tobacco after it has been processed into the finished product.¹⁰ Tolerances on tobacco have also been set in a limited number of other countries.^{11,12} Between the countries with residue tolerance regulations, there are a number of inconsistencies in the residue levels set for certain pesticides.

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The European Community (EC) is expected to consider the issue of tobacco pesticide regulation and may develop uniform standards by 1992. If the EC adopts a directive for tobacco that establishes standardized tolerances, it may include pesticides currently regulated in Germany and other EC Member States.¹²

In the United States, the use of pesticides on all agricultural products, including tobacco, is approved and otherwise regulated principally by the Environmental Protection Agency (EPA). The U.S. Department of Agriculture (USDA) also has certain regulatory responsibilities in this area.¹³ In order for their crops to qualify for the government price support program, U.S. tobacco farmers must certify that they have used only approved pesticides in accordance with specific application requirements.

Advances in Detection of Pesticide Residues

During the last several years, pesticide residues in food and drinking water have been the subject of numerous publications in technical journals and in the lay press. Among the most prominent factors contributing to public awareness on this subject are the tremendous advances in analytical science that have occurred in the last two decades. Technological developments in analytical instrumentation and methodology have made it possible to detect

extremely small residues of pesticides in a variety of commodities that were virtually undetectable only a few years ago.

It is difficult for the non-scientist to comprehend the significance of chemicals detectable at levels of parts per million, parts per billion and parts per trillion in agricultural products, water supplies and other products intended for human consumption. For example, it is important for the public to understand that one part per million is the equivalent of one second in twelve days or one centimeter in 10.3 kilometers (one inch in sixteen miles). Soon, analytical methods may make it feasible to detect residues at the level of parts per quadrillion, (the equivalent of one centimeter in 10,300,000,000 kilometers (1 inch in 16,000,000,000 miles) or 1 second in 32,000,000 years) which may have the effect of further intensifying public concern because it likely will be possible to detect residues in almost everything. Even though technology permits the detection of these extremely small quantities, such findings do not mean that pesticide residues detected at these levels have any significance in terms of health or environment.

The response to media events, such as the finding of Alar (daminozide) residues on apples in the United States, demonstrates that most people are unaware of these facts and illustrates the almost universal and erroneous belief that all pesticides, at any

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level, are bad. The general public's fear of any detectable amount of pesticide residue, however, is seldom justified by the scientific data.

Biological Testing of Pesticide Residues in Tobacco

There are no persuasive studies that establish scientifically that pesticide residues, as they occur in cigarette smoke, cause lung cancer or other diseases in humans. In fact, after decades of research, inhalation studies in which animals have been exposed to fresh whole tobacco smoke have failed to provide experimental proof that smoking causes lung cancer.¹⁴ The reference or model cigarettes used in these animal studies were made from the same inventories of tobacco used in manufacturing commercial cigarettes which would have contained residues of pesticides also found in food and other retail consumer products. In effect, then, pesticides commonly used on tobacco and other crops have been tested in animals by chronic smoke inhalation studies.

In addition, a research project sponsored by the U.S. government's Tobacco Working Group specifically investigated the effects of pesticides in tobacco smoke condensate. This study compared the biological activity of cigarette smoke condensate from specially grown pesticide-free tobacco with smoke condensate

from experimental cigarettes grown with commonly used pesticides. The results showed no statistically significant differences between the biological activity of smoke condensate from the pesticide-free compared to the pesticide-treated tobacco.¹⁻³

In summary, a comprehensive evaluation of the detectable residues in the cigarette smoke to which the smoker is exposed, the toxicological characteristics of a particular pesticide, and the results of experimental tests with cigarette smoke that contains pesticide residues does not establish a scientific basis for claims that pesticide residues in tobacco contribute to the health risks which have been associated with smoking.

Conclusion

The use of approved pesticides is necessary to achieve efficient and cost-effective production for the farmer and, ultimately, an affordable product for the consumer. Pesticide residues in agricultural products are an unavoidable by-product of the widespread use of pesticides by farmers. Compared to naturally-occurring pesticides in plants, "synthetic" pesticides constitute only a tiny fraction of the chemicals to which humans are exposed in their daily diets. There are no persuasive scientific studies which establish that the very small amounts of pesticide residues

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that have been detected in cigarette smoke are a cause of disease in smokers.

REFERENCES

1. U.S. Department of Health, Education and Welfare, Public Health Service, National Institutes of Health, Report No. 4. Toward Less Hazardous Cigarettes: The Fourth Set of Experimental Cigarettes, G.B. Gori (ed.), National Cancer Institute, Smoking and Health Program, 1-213, March, 1980.
2. U.S. Department of Health, Education and Welfare, Public Health Service, National Institutes of Health, Report No. 5. Toward Less Hazardous Cigarettes: Summary: Four Skin Painting Bioassays Using Condensate from Experimental Cigarettes, National Cancer Institute, Smoking and Health Program, 1-29, September, 1980.
3. Tso, T.C., Chaplin, J.F., LeLacheur, K.E. and Sheets, T.J., "Pesticide-treated vs. 'Pesticide-free' Tobacco: I. Tobacco Production and Leaf Analysis," Beiträge zur Tabakforschung International 10(2): 114-119, July, 1980.
4. Ames, B.N., Profet, M. and Gold, L.S., "Dietary Pesticides (99.99% All Natural)," Proceedings of the National Academy of Sciences USA 87: 7777-7781, October, 1990.
5. Paracelsus (Theoprastus ex Hohenheim Eremita): Von der Besucht, Dillingen, 1567.

6. Doull, J. and Bruce M.C., "Chapter 1. Origin and Scope of Toxicology." In: Casarett & Doull's Toxicology. The Basic Science of Poisons. Third Edition. New York, Macmillan Publishing Company, 3-10 (see particularly 3), 1986.
7. Haeberer, A.F. and Chortyk, O.T., "Gas-Liquid Chromatographic Determination of Maleic Hydrazide in Tobacco and Tobacco Smoke," Journal of the Association of Official Analytical Chemists 62(1): 171-175, 1979.
8. U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health, The Health Consequences of Smoking. The Changing Cigarette: A Report of the Surgeon General, DHHS Publication No. (PHS) 81-50156, Washington, D.C., U.S. Government Printing Office, 55, 1981.
9. U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health, The Health Consequences of Smoking. Cancer: A Report of the Surgeon General, Washington, D.C., U.S. Government Printing Office, DHHS Publication No. (PHS) 82-50179, 197, 1982.

10. "Verordnung über Höchstmengen an Pflanzenschutz und sonstigen Mitteln sowie anderen Schädlingsbekämpfungsmitteln in oder auf Lebensmitteln und Tabakerzeugnissen," Bundesgesetzblatt, June 24, 1982, and modifications, April 17, 1984; April 25, 1988, and May 5, 1989.
11. Laws and Decrees, Ministry of Health, Gazzetta Ufficiale (Supplement), No. 202, Rome, August 30, 1990.
12. Sheets, T.J., "Current Regulations on Pesticide Residues in Tobacco," Tobacco International 191(18): 21-24, October, 1989.
13. Amendment to 7 CFR Part 29, Subpart B - Regulations, "Tobacco Inspection; Flue-Cured and Burley Tobacco; Importation Prohibitions," Federal Register 54(110): at 24661-24664, June 9, 1989 (codified in the Code of Federal Regulations, Title 7, Part 29, Subpart B).
14. Cross, F.T., Dagle, G.E. and Gies, R.A., "Reply to Dr. Archer's Comment on 'A Histological Study of the Influence of Cigarette Smoking in Suppressing Rn Daughter Carcinogenesis in Dogs,'" Letter to the Editor, Health Physics 56(2): 256, February, 1989.

PESTICIDES

CLAIMS/RESPONSES

CLAIM: Cigarette manufacturers use tobacco which contains pesticides that are harmful to smokers.

RESPONSE: Pesticides are widely used in the production of farm crops throughout the world, because these chemicals help control insects, weeds, and other pests that cause substantial losses. Consequently, small amounts of residues from these substances are found in virtually all the food we eat. Pesticides used in growing these food commodities are also used in growing tobacco.

There are no persuasive scientific studies which establish that the small amounts of residues that have been detected in tobacco products are a cause of disease in smokers.¹⁻³ In fact, after decades of research, inhalation studies in which animals have been exposed to fresh whole tobacco smoke have failed to provide experimental proof that smoking causes lung cancer.⁴ The reference or model cigarettes used in those animal studies were made from the same tobacco used to make commercial cigarettes which would have contained residues of pesticides also found in food and other consumer products. In effect, then, many pesticides commonly used on tobacco and other crops

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have been tested in animals by chronic smoke inhalation studies and have not been scientifically demonstrated to be cause lung cancer.

Furthermore, in response to environmental and health concerns, many governments extensively regulate pesticide use. These regulations are designed to assure that pesticide residues present in food products and other consumables occur at levels which will not result in harm to the consumer.

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REFERENCES

1. U.S. Department of Health, Education and Welfare, Public Health Service, National Institutes of Health, Report No. 4. Toward Less Hazardous Cigarettes: The Fourth Set of Experimental Cigarettes, G.B. Gori (ed.), National Cancer Institute, Smoking and Health Program, 1-213, March, 1980.
2. U.S. Department of Health, Education and Welfare, Public Health Service, National Institutes of Health, Report No. 5. Toward Less Hazardous Cigarettes: Summary: Four Skin Painting Bioassays Using Condensate from Experimental Cigarettes, National Cancer Institute, Smoking and Health Program, 1-29, September, 1980.
3. Tso, T.C., Chaplin, J.F., LeLacheur, K.E. and Sheets, T.J., "Pesticide-treated vs. 'Pesticide-free' Tobacco: I. Tobacco Production and Leaf Analysis," Beiträge zur Tabakforschung International 10(2): 114-119, July, 1980.
4. Cross, F.T., Dagle, G.E. and Gies, R.A., "Reply to Dr. Archer's Comment on 'A Histological Study of the Influence of Cigarette Smoking in Suppressing Rn Daughter Carcinogenesis in Dogs,'" Letter to the Editor, Health Physics 56(2): 256, February, 1989.

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CLAIM: Pesticides must be harmful, regardless of how little there is in a product. Why else would the media pay so much attention to reports that there are pesticides in food?

RESPONSE: Technological developments have made it possible to detect extremely small residues of pesticides that were virtually undetectable only a few years ago. However, simply because it is possible to detect small amounts of a substance in, for example, a food product does not establish that it is hazardous. The mechanism that makes pesticides effective in controlling various pests and weeds does not automatically translate into health concerns or an adverse impact on the environment. Orchestrated events such as the "Alar scare" in the U.S. suggest that the media may report the news before all scientific facts have been considered.

In this regard, it is worth considering that nature is the major source of plant defense chemicals. Grain, fruit, and vegetable plants have protective mechanisms that produce chemical defenses against infestation by insects, fungi and animal predators. It has been estimated, for example, that an average American may consume about 10,000 times more natural "pesticides" per day than synthetic or man-made pesticide residues. In

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other words, 99.9% of the pesticide chemicals consumed through the diet are naturally occurring.¹

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REFERENCES

1. Ames, B.N., Profet, M. and Gold, L.S., "Dietary Pesticides (99.99% All Natural)," Proceedings of the National Academy of Sciences USA 87: 7777-7781, October, 1990.

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CORONARY HEART DISEASE: EXECUTIVE SUMMARY

Based primarily on statistical reports, claims are often made that cigarette smoking is a major cause of coronary heart disease (CHD), which occurs when the heart does not receive enough oxygen. Despite such allegations, however, a careful review of the literature on CHD demonstrates that the causes of CHD are still not well understood. This literature also demonstrates that there is much that is unknown about what role, if any, smoking may play in its development. In fact, when the literature on tobacco and CHD is critically reviewed, a number of perplexing and unresolved paradoxes surface. For example, smoking is only one of many statistical associations, termed "risk factors," that have been reported for heart disease. Moreover, reductions in such risk factors have not been demonstrated to lead to corresponding reductions in heart disease mortality rates. In addition, there are a variety of inconsistencies and anomalies in the statistical studies of smoking and CHD. Finally, scientists have not been able to establish what, if anything, in cigarette smoke is related to the development of CHD. Accordingly, it is readily apparent that cigarette smoking has not been proven to cause CHD.

The claim that smoking is a risk factor for CHD refers to reports that smokers have a statistically increased risk of the disease. However, it is important not to confuse risk factors with causal factors because, among other reasons, statistical associations cannot provide information on biological processes

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whereby a factor, such as smoking, might lead to heart disease. Thus, such associations, by themselves, cannot establish a causal relationship.

Furthermore, smoking is only one of hundreds of other factors that have been reported to be statistically related to CHD. A few of the most well-known of these include gender (males are more likely to develop CHD than females), genetics, elevated blood levels of cholesterol, high blood pressure, diet, obesity, physical inactivity and stress. Additional risk factors continue to appear in the literature. Yet, which, if any, of these may have causal significance is not known. Certainly, however, there is reason to question their significance in view of the failure of so-called intervention trials to demonstrate that reductions in levels of risk factors, including smoking, lead to reductions in CHD mortality risk.

There are also notable inconsistencies and anomalies in many of the studies reporting associations of smoking and CHD, again, calling into question the claim that smoking causes CHD. For example, some studies, particularly those of women, do not even report a statistical relationship between smoking and CHD. Others indicate that any statistical relationship between smoking and heart disease may be observable only in groups with a high fat or cholesterol intake. It is also a statistical paradox that trends in CHD rates over time are sometimes reported to be inconsistent

with trends in cigarette smoking. In recent decades, for example, trends in CHD rates have been reported to be increasing in some countries and decreasing in others, apparently with little or no relationship to changes in smoking.

Claims that smoking causes CHD often rely strongly on still other reports that quitting smoking reduces the risk for this disease. It is important to recognize that comparisons of the CHD rates of smokers and exsmokers would be valid only if it were assumed that these groups were the same in all respects except for their smoking habits. This assumption is false, however, as demonstrated by studies from a variety of countries, including Britain, the United States, Japan, and Finland, which report that exsmokers differ from smokers in fundamental, even possibly genetic, ways. In fact, these studies suggest that exsmokers tend to be more like nonsmokers even before they quit smoking.

Finally, the claim is sometimes made that certain constituents in cigarette smoke, specifically carbon monoxide (CO) and nicotine, have adverse effects on the cardiovascular system. Various theories have been discussed about how these substances could exert an effect. However, despite the intensive research to which tobacco smoke has been subjected over many years, these constituents, as found in cigarette smoke, have not been scientifically proven to cause CHD.

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In conclusion, many questions and paradoxes remain unanswered about the possible nature of the role, if any, that smoking may have in the development of CHD. These paradoxes reflect a challenge that only continued research can resolve. Perhaps what is most apparent from the literature is that the causes of heart disease are likely to be numerous and complicated, and that claims focusing on a single factor, such as smoking, should be regarded with considerable skepticism.

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CORONARY HEART DISEASE

Heart disease is one of the leading causes of death in many countries and, perhaps as a result, it has been the subject of intensive scientific study for many years. Although much has been learned during this time, the causes of heart disease are not known. Nevertheless, based primarily on statistical reports, claims are often made that cigarette smoking is a major cause of diseases of the heart, in particular coronary heart disease (CHD), which occurs when the heart does not receive enough oxygen.

Despite such allegations, the literature on CHD demonstrates that there is much that is unknown about what role, if any, smoking may play in its development. In fact, a group of United States physicians recently concluded that when the literature on tobacco and CHD is reviewed critically, "a number of perplexing and as yet unresolved paradoxes painfully surface."¹ For example, although not generally mentioned by anti-smokers, cigarette smoking is only one of many statistical associations, termed "risk factors," that have been reported for heart disease. Others frequently discussed are high blood pressure and elevated blood cholesterol levels. Nor is it generally mentioned by anti-smokers that reductions in such risk factors have not been demonstrated to lead to corresponding reductions in heart disease mortality rates. In addition, there are numerous inconsistencies and anomalies in the epidemiological (population or statistical) studies of smoking and

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CHD. Finally, scientists have not been able to establish what, if anything, in cigarette smoke is related to the development of CHD. Accordingly, it is readily apparent that cigarette smoking has not been proven to cause CHD.

Risk Factors

Smoking is often regarded as a risk factor for CHD because smokers are reported to have a statistically increased risk of the disease. However, risk factors do not necessarily imply cause-and-effect. As a literature review from the University of Oslo, Norway, pointed out, "risk factors should not be confused with causal factors."² That is because, among other reasons, statistical associations cannot provide information on biological processes whereby a factor, such as smoking, might lead to heart disease.

Most investigators seem to be aware of the limitations of statistical data. Even reports of the United States Surgeon General have recognized this. For example, the first such report, in 1964, noted that "statistical methods cannot establish proof of a causal relationship in an association."³ Similarly, in the context of discussing smoking and cardiovascular disease, the 1979 report noted that "correlation [association is a type of correlation] is not synonymous with causation."⁴ This basic tenet of scientific interpretation, though widely understood, sometimes

seems to be forgotten by antismoking advocates when assessing statistical data concerning smoking and CHD.

It is also important to recognize that smoking is only one of literally hundreds of factors that have been reported to be statistically related to CHD. Some of the most well-known of these, in addition to cigarette smoking, high blood pressure, and elevated blood cholesterol levels, are gender (males are more likely to develop CHD than females), genetics, obesity, physical inactivity, and stress. However, these are only a few of the risk factors that have been reported in the literature, and additional risk factors continue to be reported. One major survey in 1981 listed nearly 250 factors that had been reported to be related to CHD up to that time.⁵ An updated review in 1986 noted that an additional 30 to 40 risk factors had been reported since the earlier review and that the literature on risk factors "seems to expand at almost an exponential rate."⁶ Although these authors consider smoking to be one of the most important risk factors, whether or which of these may have causal significance is unknown, as the following discussion illustrates.

Genetics

One of the most widely discussed CHD risk factors is genetics or heredity. A number of researchers have speculated that this factor may explain why CHD rates tend to be higher in

certain families, geographic areas and ethnic groups. The potential role of genetics was considered in detail in two major literature reviews by Drs. Neufeld and Goldbourt, scientists at Israel's Tel Aviv University. In their first review published in 1983, they noted that variations in risk factors, including smoking, could not satisfactorily account for differences in CHD rates in different groups but that genetics play a "significant" role "in determining the degree, time course and severity of the atherosclerotic process and the occurrence of symptomatic CHD."⁷ In their second review published three years later, they focused on the genetic aspects of atherosclerosis, a narrowing of the arteries which is often an important underlying condition in the development of CHD. Although they cautioned that "speculations still exceed concrete knowledge" about this disease process, they nevertheless emphasized that genetics is given a potentially important role in its development in the literature.⁸

The apparent importance of genetics in CHD development was also emphasized by the late Philip R.J. Burch, an eminent medical physicist from the United Kingdom's University of Leeds. Based on his analysis of data from several major types of epidemiological studies, he concluded that none of these studies "endorses the idea that the classical 'risk factors' -- except, of course, the familial (genetic) one -- exert any appreciable causal action. Claims to the contrary are based on uncritical evidence and faulty logic."⁹

Stress and Personality

Many studies suggest that people with a certain type of personality are prime candidates for developing CHD. Such persons tend to be hard-driving, time-conscious, often impatient and emotionally tense, characteristics that are likely to promote a stressful lifestyle. No one knows why some persons have such a personality, although it has been speculated that it may have to do with personal preference or some relatively unalterable trait that they are born with. For whatever reason, in most industrialized countries which tend to have the highest CHD rates, many people lead very stressful lives.

One of the most widely discussed aspects of personality in relation to heart disease is the so-called type A versus type B behavior pattern. The pioneers in researching this concept are Drs. Meyer Friedman and Ray Rosenman, who brought these behavior patterns to the attention of the medical community in a 1959 report in the Journal of the American Medical Association. On the basis of their research, they characterized persons with a "type A" behavior pattern as very achievement-oriented, usually toward poorly defined goals, constantly busy, always feeling a sense of urgency about time, alertness and a desire for recognition and advancement. Persons with a "type B" behavior pattern, on the other hand, were generally characterized as having a relative absence of these

characteristics. When Friedman and Rosenman compared the CHD rates of men with "type A" versus "type B" behavior patterns, they found a "startling difference." Men with "type A" behavior were seven times more likely to have heart disease than men with "type B."¹⁰

Since its introduction, the "type A" concept has been extensively studied and refined by many researchers and investigators. Friedman argues that their findings have strongly confirmed the role of this behavior pattern in CHD.¹¹ Much of the recent literature in this area has focused on more specific personality and stress-related characteristics that might be part of a broad personality type such as "type A" or "type B." For example, researchers have reported that "hostility,"¹² "time urgency"¹³ and "severe anxiety"¹⁴ are associated with CHD.

Reports of what patients say they are experiencing at the time they have a heart attack are consistent with the epidemiological literature associating CHD with personality and stress. For example, an intriguing clinical study from the United States reported that mental stress may, in fact, act as a potential trigger for a heart attack. When nearly 850 heart attack patients were asked about the events that preceded their heart attacks, their most commonly reported potential trigger was "emotional upset."¹⁵

A possible relationship between behavioral characteristics and CHD has also been supported by the results of animal research. In the United States, an experiment with monkeys at a North Carolina school of medicine reportedly demonstrated that animals exposed to unstable, stressful social conditions had increased development of coronary artery atherosclerosis. The researchers conducting the experiment concluded that these data were "consistent" with "current hypotheses concerning the role of individual behavioral characteristics in the development of coronary disease in humans."¹⁶ In a subsequent study by this same research group, it was reported that monkeys that were relatively more "reactive" to stress as measured by increases in heart rate developed more atherosclerosis.¹⁷ Some animal research reports have even suggested biological mechanisms that might explain how behavioral or personality factors could lead to CHD. For example, Dr. William Gutstein, of the New York Medical College, has reported that electrical stimulation of those parts of the brain that may be involved in the body's response to stress can damage the arteries and induce atherosclerosis.¹⁸

Intervention Trials

Additional questions regarding the significance of risk factors are raised by the results of risk factor intervention trials. These trials are a type of epidemiological study in which attempts are made to test the theory that reductions in risk

factors, including smoking, will lead to reductions in CHD mortality risk. In such a study, an investigator randomly assigns each participant to either an intervention or a control group. Those in the intervention group receive special assistance in lowering their risk factor levels, for example, to reduce smoking. Their subsequent CHD rates are then compared to those in the control group who did not receive any special assistance.

Despite massive and costly research efforts in numerous countries, intervention trials have failed to establish that lowering risk factor levels reduces CHD mortality risk. The largest of these studies was conducted under the auspices of the World Health Organization in five European countries -- the United Kingdom, Belgium, Italy, Poland and Spain.¹⁹ Other large-scale European trials were performed in Norway²⁰ and England.²¹

The largest effort undertaken in a single country is the United States' Multiple Risk Factor Intervention Trial, known as MRFIT. MRFIT was designed to examine whether reductions in cigarette smoking, high blood pressure and elevated serum cholesterol would reduce the risk of CHD mortality. Although the participants in the study were successful in reducing the levels of these risk factors, the seven-year follow-up failed to demonstrate that reducing these risk factors significantly reduces the chances of dying from coronary heart disease.²² Even after a

10-year follow-up, no statistically reliable overall effect on CHD mortality was reported.²³

Some researchers apparently have had difficulty accepting weaknesses in the intervention trial data. This was a central point in a review of CHD intervention trials by two Irish researchers. James McCormick and Petr Skrabanek, of the University of Dublin, noted that "[d]espite this considerable body of evidence which shows no benefits for intervention, many have interpreted the results as supportive of their wishful thinking."²⁴ They cited the example of the WHO study which they pointed out showed "no difference" in CHD mortality between the control and the intervention groups, yet the authors attempted to give their reported results public health importance. As McCormick and Skrabanek pointed out, "It would appear that statistical evaluation can be disregarded if it does not support a forgone conclusion."²⁵

Viewed together, the risk factor intervention studies represent a variety of different methodologies and study populations. Yet, each one has reported basically similar results -- namely, the failure to demonstrate statistically significant reductions in CHD mortality attributable to reductions in smoking.

Inconsistencies and Anomalies

There are notable inconsistencies and anomalies in many of the studies reporting associations between smoking and CHD. For example, the potential statistical association is sometimes reported to be weak or not even present; trends in CHD rates are not explained by changes in smoking consumption; and studies of CHD rates in exsmokers have serious methodological flaws.

Weaknesses in Association

Some studies do not even report a statistical relationship between smoking and CHD. In Busselton, Western Australia, for example, a large-scale prospective study reported no significant association between CHD and smoking. Although the authors did report that smoking was associated with some disease or mortality outcomes, nevertheless, they commented that smoking "was unrelated to CVD [cardiovascular disease] and CHD in either men or women."²⁶

Studies of women, in particular, have raised questions about a statistical association between smoking and CHD. For example, in a prospective study of women in Gothenburg, Sweden, researchers reportedly found "no significant increased risk" of CHD in smoking women.²⁷ In the United States, even the Framingham Heart Study, perhaps the largest and most well-known prospective

epidemiological study of coronary heart disease risk factors, noted a strong gender difference in any CHD/smoking association. That is, while reports from this study have generally argued for the importance of smoking as a CHD risk factor, it also has been reported that, at least for CHD mortality in women, "no significant relationship can be shown."²⁸ In fact, on the basis of such apparent gender differences, and on other anomalies in the data, a researcher from Harvard University has suggested that the Framingham Heart Study results in general "are inconsistent with the Surgeon General's views about cigarette smoking and coronary heart disease."²⁹

The interpretation of the statistical data on smoking and heart disease is further complicated by reports that this relationship may be observable only in groups with a high fat or cholesterol intake. In fact, the editor of an American medical journal dedicated to the study of the diseases and functioning of the heart has argued that an elevated cholesterol level is the most important factor in the development of heart disease. Although he views smoking as having a role in the development of CHD in individuals with high cholesterol levels, he does not consider it to be an "independent" risk factor.³⁰ To support this opinion, he cited the experience of the Japanese who are well-known for their low rates of heart disease despite their widespread cigarette smoking, and their low fat and cholesterol diet. Others have also cited the Japanese example as suggesting that cigarette smoking is

"a weak or nonexistent risk factor for heart attack if atherosclerosis from a high cholesterol diet is absent."³¹ Obviously, such reported findings must be taken into account in evaluating the literature on smoking and heart disease.

Trends

It is also a statistical paradox that trends in CHD rates over time do not correspond closely with trends in cigarette smoking. In recent decades, for example, CHD rates have reportedly been increasing in some countries and decreasing in others, but such trends have not been shown to be explained by changes in smoking. A report from St. Thomas's Hospital Medical School, in London, for example, observed that since about 1968, CHD mortality has been decreasing in the United States, Canada and some western European countries. However, when these decreases in CHD were compared to changes in fat intake and smoking habits, it was determined that "the change in fat intake rather than smoking habits would appear to be the likely reason for the decline in CHD."³²

On the other hand, an upward trend in CHD mortality rates was observed in a study of Swedish males during the same time period that their prevalence of smoking decreased. The authors of this study commented that the increase in CHD mortality was apparent in their study, even though "all" the changes in smoking, exercise, and blood pressure treatment that have been used to explain

decreases in CHD mortality in other countries "also apply to Sweden."³³

Exsmoker Studies

Claims that smoking causes CHD often rely strongly on reports that quitting smoking reduces the risk for this disease. Such claims rely on the assumption that smokers and exsmokers are the same in all respects except for their smoking habits. This is a false assumption, however, as demonstrated by studies from many countries, including Britain,³⁴ the United States,³⁵ Japan³⁶ and Finland,³⁷ which show that exsmokers differ from smokers in fundamental, even possibly genetic, ways. In fact, those studies show that exsmokers tend to be more like nonsmokers even before they quit smoking.

Perhaps the most comprehensive examination of the characteristics of exsmokers was conducted as part of a large-scale ongoing research project in the United States involving California members of Kaiser Permanente, a private health care insurance plan. In that study, a large number of traits and characteristics including many believed to be related to the development of heart disease were measured in groups of smokers, nonsmokers and exsmokers before the exsmokers quit. It was reported that "smokers who later quit showed statistically significant differences from smokers who continued smoking, in certain cardiovascular symptoms, social and

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personal characteristics, smoking intensity, and some other traits."³⁸

There is disagreement in the scientific world about the significance of the differences between smokers and exsmokers and how those differences should be interpreted. It has been suggested, for example, that the characteristics of exsmokers put them at a decreased risk of CHD even before they quit smoking.³⁹ Others have suggested that the characteristics which appear to put exsmokers at decreased risk are "compensated for" by others which may put them at higher risk.⁴⁰ These sorts of disagreements indicate the need for further research to obtain a better understanding of the differences between smokers and exsmokers and the possible relationship of those differences to CHD.

Carbon Monoxide and Nicotine

The claim is sometimes made that certain constituents in cigarette smoke, specifically carbon monoxide (CO) and nicotine, have adverse effects on the cardiovascular system. Various theories have been discussed about how these substances could exert an effect. It has been speculated, for example, that both these constituents might increase the rate of the development of atherosclerosis or that they may alter the balance of oxygen supply and demand, thus precipitating angina pectoris (heart pain) or a heart attack. However, despite the intense research to which

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tobacco smoke has been subjected over many years, these constituents as found in cigarette smoke have not been scientifically proven to cause coronary heart disease.

Claims that carbon monoxide in cigarette smoke may be involved in the development of CHD have frequently emphasized the early results of a team of Danish researchers.⁴¹ Their research involved exposing rabbits to carbon monoxide for long periods of time and then microscopically examining the arteries to see if any changes had occurred. In their initial studies, they reported vascular changes which they thought were similar to early stages of atherosclerosis in humans. However, when they repeated the experiments (because they thought their initial studies may have been flawed), they were unable to find a toxic effect of carbon monoxide.⁴² These and other weaknesses in the data were noted in a subsequent review of a wide variety of literature relating to carbon monoxide from the School of Public Health at the University of Texas Health Science Center, Houston. The review concluded that the concern which has sometimes been expressed about possible effects of CO exposure on the cardiovascular system "is largely unwarranted."⁴³

Even the 1983 U.S. Surgeon General's Report, which was the only report to focus exclusively on cardiovascular disease, expressed a number of important reservations about the data on carbon monoxide and nicotine in relation to this disease. For

example, the Report observed that animal experiments on atherosclerosis and carbon monoxide "must be considered to be unsatisfactory."⁴⁴ With regard to nicotine, the Report conceded that "the evidence for and against a primary role for nicotine in the development or acceleration of atherosclerosis is not conclusive."⁴⁵ Furthermore, it stated that a "mechanism whereby nicotine can trigger a cardiovascular event is unknown."⁴⁶

Similar conclusions were reached in the United Kingdom by an independent scientific committee in a report to the government. Although the committee report asserted that smoking has adverse health effects and that CO and nicotine may be involved, it nevertheless noted several weaknesses in the literature. For example, the report stated that nicotine, at levels in cigarette smoke, "has not been shown to harm the cardiovascular system in healthy people."⁴⁷ Regarding carbon monoxide and heart disease, the report noted that the literature has "not clearly established" that it is a causal factor.⁴⁸

Conclusion

Many questions remain unanswered about the possible nature of the role, if any, that smoking may have in the development of CHD. These questions reflect a challenge that only continued research can resolve. Perhaps what is most apparent from the literature is that the causes of heart disease are likely to be

numerous and complicated, and that claims focusing on a single factor, such as smoking, should be regarded with considerable skepticism.

REFERENCES

1. Brockie, R.E., Shafer, D.R. and Huber, G.L., "Tobacco and Coronary Heart Disease: Risk Factors, Mechanisms of Disease, and Risk Modification," Seminars in Respiratory Medicine 11(1): 5-35 (at 7), 1990.
2. Kringlen, E., "Coronary Heart Disease. Social Causation?" Psychiatry and Social Science 2: 5-22 (at 9), 1982.
3. U.S. Department of Health, Education, and Welfare, Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service. Publication No. (PHS) 1103, Washington, D.C., U.S. Government Printing Office, (at 20), 1964.
4. U.S. Department of Health, Education, and Welfare, Smoking and Health: A Report of the Surgeon General. Publication No. (PHS) DHEW 79-50066, Washington, D.C., U.S. Government Printing Office, (at 4-65), 1979.
5. Hopkins, P.N. and Williams, R.R., "A Survey of 246 Suggested Coronary Risk Factors," Atherosclerosis 40: 1-52, 1981.
6. Hopkins, P.N. and Williams, R.R., "Identification and Relative Weight of Cardiovascular Risk Factors," Cardiology Clinics 4(1): 3-31 (at 4), 1986.
7. Neufeld, H.N. and Goldbourt, U., "Coronary Heart Disease: Genetic Aspects," Circulation 67(5): 943-954 (at 943), 1983.
8. Goldbourt, U. and Neufeld, H.N., "Genetic Aspects of Arteriosclerosis," Arteriosclerosis 6(4): 357-377 (at 357), 1986.
9. Burch, P.R.J., "Ischaemic Heart Disease: Epidemiology, Risk Factors and Cause," Cardiovascular Research 14: 307-338 (at 336), 1980.
10. Friedman, M. and Rosenman, R.H., "Association of Specific Overt Behavior Pattern With Blood and Cardiovascular Findings," Journal of the American Medical Association, 169(12): 1286-1296 (at 1295), 1959.
11. Friedman, M., "Type A Behavior: A Frequently Misdiagnosed and Rarely Treated Medical Disorder," American Heart Journal 115(4): 930-936, 1988.
12. Dembroski, T.M., MacDougall, J.M., Costa, P. T. and Grandits, G.A., "Components of Hostility as Predictors of Sudden Death and Myocardial Infarction in the Multiple Risk Factor

10379248

- Intervention Trial," Psychosomatic Medicine 51: 514-522, 1989.
13. Levine, R.V., Lynch, K., Miyake, K. and Lucia, M., "The Type A City: Coronary Heart Disease and the Pace of Life," Journal of Behavioral Medicine 12(6): 509-524, 1989.
 14. Russek, L.G., King, S.H., Russek, S.J. and Russek, H.I., "The Harvard Mastery of Stress Study 35-Year Follow-up: Prognostic Significance of Patterns of Psychophysiological Arousal and Adaptation," Psychosomatic Medicine 52: 271-285, 1990.
 15. Tofler, G.H., Stone, P.H., Maclure, M., Edelman, E., Davis, V.G., Robertson, T., Antman, E.M., Muller, J.E. and the MILIS Study Group, "Analysis of Possible Triggers of Acute Myocardial Infarction (The MILIS Study)," The American Journal of Cardiology 66: 22-27, 1990.
 16. Kaplan, J.R., Manuck, S.B., Clarkson, T.B., Lusso, F.M. and Taub, D.M., "Social Status, Environment, and Atherosclerosis in Cynomolgus Monkeys," Arteriosclerosis 2: 359-368 (at 366), 1982.
 17. Manuck, S.B., Kaplan, J.R., Adams, M.R. and Clarkson, T.B., "Behaviorally Elicited Heart Rate Reactivity and Atherosclerosis in Female Cynomolgus Monkeys (*Macaca fascicularis*)," Psychosomatic Medicine 51(3): 306-318, 1989.
 18. Gutstein, W.H., "The Central Nervous System and Atherogenesis: Endothelial Injury," Atherosclerosis 70: 145-154, 1988.
 19. World Health Organization European Collaborative Group, "Multifactorial Trial in the Prevention of Coronary Heart Disease: 3. Incidence and Mortality Results," European Heart Journal 4: 141-147, 1983.
- World Health Organisation European Collaborative Group, "European Collaborative Trial of Multifactorial Prevention of Coronary Heart Disease: Final Report on the 6-Year Results," The Lancet, pp. 869-872, April 19, 1986.
20. Hjermann, I., Velve Byre, K., Holme, I. and Leren, P., "Effect of Diet and Smoking Intervention on the Incidence of Coronary Heart Disease," The Lancet, pp. 1303-1310, December 12, 1981.
- Holme, I., "On the Separation of the Intervention Effects of Diet and Antismoking Advice on the Incidence of Major Coronary Events in Coronary High Risk Men," Journal of the Oslo City Hospital 32: 31-54, 1982.
21. Rose, G. and Hamilton, P.J.S., "A Randomised Controlled Trial of the Effect on Middle-Aged Men of Advice to Stop Smoking," Journal of Epidemiology and Community Health, 32(4): 275-

281, 1978.

Rose, G., Hamilton, P.J.S., Colwell, L. and Shipley, M.J., "A Randomised Controlled Trial of Anti-Smoking Advice: 10-Year Results," Journal of Epidemiology and Community Health 36: 102-108, 1982.

22. Multiple Risk Factor Intervention Trial Research Group, "Multiple Risk Factor Intervention Trial. Risk Factor Changes and Mortality Results," Journal of the American Medical Association 248(12): 1465-1477, 1982.
23. The Multiple Risk Factor Intervention Trial Research Group, "Mortality Rates After 10.5 Years for Participants in the Multiple Risk Factor Intervention Trial," Journal of the American Medical Association 263(13): 1795-1801, 1990.
24. McCormick, J. and Skrabanek, P., "Coronary Heart Disease is not Preventable by Population Interventions," The Lancet II: 839-841 (at 840), October 8, 1988.
25. McCormick, J. and Skrabanek, P., "Coronary Heart Disease is not Preventable by Population Interventions," The Lancet II: 839-841 (at 840), October 8, 1988.
26. Cullen, K., Stenhouse, N.S., Wearne, K.L. and Welborn, T.A., "Multiple Regression Analysis of Risk Factors for Cardiovascular Disease and Cancer Mortality in Busselton, Western Australia -- 13-Year Study," Journal of Chronic Diseases 36(5): 371-377 (at 374), 1983.
27. Lapidus, L., Bengtsson, C., Lindquist, O., Sigurdsson, J.A. and Rafnsson, V., "Smoking -- A Risk Factor for Cardiovascular Disease in Women?" Scandinavian Journal of Primary Health Care 4(4): 219-224 (at 219), 1986.
28. Kannel, W.B., "Update on the Role of Cigarette Smoking in Coronary Artery Disease," American Heart Journal 101(3): 319-328 (at 319), 1981.
29. Seltzer, C.C., "Framingham Study Data and 'Established Wisdom' About Cigarette Smoking and Coronary Heart Disease," Journal of Clinical Epidemiology 42(8): 743-750 (at 743), 1989.
30. Roberts, W.C., "Atherosclerotic Risk Factors -- Are There Ten or Is There Only One?" The American Journal of Cardiology 64(8): 552-554 (at 553), 1989.
31. Kuller, L.H., "An Epidemiologist Looks At Risk Assessment," Health & Environment Digest 1(10): 1-3 (at 2), 1987.

10379248

32. Heller, R.F., "The Declining Mortality from CHD," Journal of the Royal College of Physicians of London 17(1): 73, 1983.
33. Welin, L., Wilhelmsen, L., Svärdsudd, K., Larsson, B. and Tibblin, G., "Increasing Mortality from Coronary Heart Disease among Males in Sweden," Cardiology 72(1/2): 75-80 (at 78), 1985.
34. Eysenck, H.J., "The Effects of Giving Up Smoking." In: The Causes and Effects of Smoking, Beverly Hills, California, Sage Publications, Appendix C, 339-357 (at 346), 1980.
35. Thomas, C.B., "Personality Differences Between Smokers and Nonsmokers," Maryland Medical Journal 27(5): 63-66 (at 65), 1978.
36. Kato, I., Tominaga, S. and Suzuki, T., "Characteristics of Past Smokers," International Journal of Epidemiology 18(2): 345-354 (at 345), 1989.
37. Kaprio, J. and Koskenvuo, M., "A Prospective Study of Psychological and Socioeconomic Characteristics, Health Behavior and Morbidity in Cigarette Smokers Prior to Quitting Compared to Persistent Smokers and Non-Smokers," Journal of Clinical Epidemiology 41(2): 139-150, 1988.
38. Friedman, G.D., Siegelau, A.B., Dales, L.G. and Seltzer, C.C., "Characteristics Predictive of Coronary Heart Disease in Ex-Smokers Before They Stopped Smoking: Comparison with Persistent Smokers and Nonsmokers," Journal of Chronic Diseases 32(112): 175-190 (at 175), 1979.
39. Seltzer, C.C., "Smoking and Coronary Heart Disease: What Are We to Believe?" American Heart Journal 100(3): 275-280, 1980.
40. Friedman, G.D., Petitti, D.B., Bawol, R.D. and Siegelau, A.B., "Mortality in Cigarette Smokers and Quitters," New England Journal of Medicine 304(23): 1407-1410, 1981.
41. Astrup, P., Kjeldsen, K. and Wanstrup, J., "Enhancing Influence of Carbon Monoxide on the Development of Atheromatosis in Cholesterol-Fed Rabbits," Journal of Atherosclerosis Research 7: 343-354, 1967.
- Wanstrup, J., Kjeldsen, K. and Astrup, P., "Acceleration of Spontaneous Intimal-Subintimal Changes in Rabbit Aorta by a Prolonged Moderate Carbon Monoxide Exposure," Acta Pathologica, Microbiologica et Immunologica Scandinavica 75: 353-362, 1969.
42. Stender, S., Astrup, P. and Kjeldsen, K., "The Effect of Carbon Monoxide on Cholesterol in the Aortic Wall of Rabbits," Atherosclerosis 28: 357-367, 1977.

10379248

Hugod, C., Hawkins, L.H., Kjeldsen, K., Thomsen, H.K. and Astrup, P., "Effect of Carbon Monoxide Exposure on Aortic and Coronary Intimal Morphology in the Rabbit," Atherosclerosis 30: 333-342, 1978.

Hugod, C. and Astrup, P., "Exposure of Rabbits to Carbon Monoxide and other Gas Phase Constituents of Tobacco Smoke," Münchener medizinische Wochenschrift: S 18-S 24, 1980.

43. Weir, F.W. and Fabiano, V.L., "Re-Evaluation of the Role of Carbon Monoxide in Production or Aggravation of Cardiovascular Disease Processes," Journal of Occupational Medicine 24(7): 519-525 (at 519), 1982.
44. U.S. Department of Health and Human Services, The Health Consequences of Smoking, Cardiovascular Disease. A Report of the Surgeon General. Publication No. DHHS (PHS) 84-50204, Washington, D.C., U.S. Government Printing Office, (at 223), 1983.
45. U.S. Department of Health and Human Services, The Health Consequences of Smoking, Cardiovascular Disease. A Report of the Surgeon General. Publication No. DHHS (PHS) 84-50204, Washington, D.C., U.S. Government Printing Office, (at 50), 1983.
46. U.S. Department of Health and Human Services, The Health Consequences of Smoking, Cardiovascular Disease. A Report of the Surgeon General. Publication No. DHHS (PHS) 84-50204, Washington, D.C., U.S. Government Printing Office, (at 215), 1983.
47. U.K. Department of Health and Social Security Independent Scientific Committee on Smoking and Health, Froggatt, P., "Third Report of the Independent Scientific Committee on Smoking and Health," London, Her Majesty's Stationery Office, 1-22 (at 6), 1983.
48. U.K. Department of Health and Social Security Independent Scientific Committee on Smoking and Health, Froggatt, P., "Third Report of the Independent Scientific Committee on Smoking and Health," London, Her Majesty's Stationery Office, 1-22 (at 7), 1983.

CORONARY HEART DISEASE

CLAIMS/RESPONSES

CLAIM: Smoking causes coronary heart disease.

RESPONSE:

-- Despite many years of extensive research, scientists have not been able to determine what causes heart disease (CHD). Statements that cigarette smoking is a risk factor, meaning that smokers reportedly have a statistically increased risk of CHD, should not be confused with the more difficult question of whether this reflects biological causation. It is a well-known scientific principle that statistical associations alone cannot establish a causal relationship. And, as noted in a literature review from the University of Oslo, Norway, "there is no accepted mechanism indicating how tobacco smoking might possibly enhance CHD."¹

-- While some studies report that cigarette smoking is statistically related to CHD, the significance of such data is difficult to interpret because, in fact, literally hundreds of factors are said to have this kind of statistical relationship.² A few of the

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most well-known of these include male sex, genetics, elevated blood levels of cholesterol, high blood pressure, obesity, diet, physical inactivity and stress. Which, if any, of the hundreds of reported risk factors may have causal significance is unknown.

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REFERENCES

1. Kringlen, E., "Coronary Heart Disease. Social Causation?" Psychiatry and Social Science 2: 5-22 (at 11), 1982.
2. Hopkins, P.N. and Williams, R.R., "A Survey of 246 Suggested Coronary Risk Factors," Atherosclerosis 40: 1-52, 1981.

Hopkins, P.N. and Williams, R.R., "Identification and Relative Weight of Cardiovascular Risk Factors," Cardiology Clinics 4(1): 3-31, 1986.

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CLAIM: Quitting smoking reduces the risk of heart disease.

RESPONSE:

- Risk factor intervention trials are specifically designed to determine whether decreases in the levels of risk factors, including smoking, reduce the risk of heart disease. Despite massive and costly research efforts, intervention trials have failed to establish that decreases in risk factors lead to reductions in the risk of dying from heart disease.¹ This was a central point in an important review of CHD intervention trials by two researchers at the University of Dublin, who characterized the literature as providing a "considerable body of evidence which shows no benefits for intervention."²
- Claims that quitting smoking reduces the risk for this disease are often based on comparisons of the CHD rates of smokers and exsmokers. Such comparisons would be valid, however, only if it were assumed that these groups were equivalent except for whether they continued to smoke or quit. This assumption is false, as exsmokers reportedly differ from smokers in numerous ways. In fact, they tend to be more like nonsmokers even before they quit smoking.³

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Thus, if exsmokers have lower heart disease rates,
it may be because of the sorts of people they are,
not simply because they quit smoking.⁴

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REFERENCES

1. World Health Organization European Collaborative Group, "Multifactorial Trial in the Prevention of Coronary Heart Disease: 3. Incidence and Mortality Results," European Heart Journal 4: 141-147, 1983.

World Health Organisation European Collaborative Group, "European Collaborative Trial of Multifactorial Prevention of Coronary Heart Disease: Final Report on the 6-Year Results," The Lancet, pp. 869-872, April 19, 1986.

Hjermann, I., Velve Byre, K., Holme, I. and Leren, P., "Effect of Diet and Smoking Intervention on the Incidence of Coronary Heart Disease," The Lancet, pp. 1303-1310, December 12, 1981.

Holme, I., "On the Separation of the Intervention Effects of Diet and Antismoking Advice on the Incidence of Major Coronary Events in Coronary High Risk Men," Journal of the Oslo City Hospital 32: 31-54, 1982.

Rose, G. and Hamilton, P.J.S., "A Randomised Controlled Trial of the Effect on Middle-Aged Men of Advice to Stop Smoking," Journal of Epidemiology and Community Health, 32(4): 275-281, 1978.

Rose, G., Hamilton, P.J.S., Colwell, L. and Shipley, M.J., "A Randomised Controlled Trial of Anti-Smoking Advice: 10-Year Results," Journal of Epidemiology and Community Health 36: 102-108, 1982.

Multiple Risk Factor Intervention Trial Research Group, "Multiple Risk Factor Intervention Trial. Risk Factor Changes and Mortality Results," Journal of the American Medical Association 248(12): 1465-1477, 1982.

The Multiple Risk Factor Intervention Trial Research Group, "Mortality Rates After 10.5 Years for Participants in the Multiple Risk Factor Intervention Trial," Journal of the American Medical Association 263(13): 1795-1801, 1990.

2. McCormick, J. and Skrabanek, P., "Coronary Heart Disease is not Preventable by Population Interventions," The Lancet II: 839-841 (at 840), October 8, 1988.
3. Thomas, C.B., "Personality Differences Between Smokers and Nonsmokers," MD State Med. J. 27(5): 63-66, 1978.

Kato, I., Tominaga, S. and Suzuki, T., "Characteristics of

Past Smokers," International Journal of Epidemiology 18(2): 345-354, 1989.

Kaprio, J. and Koskenvuo, M., "A Prospective Study of Psychological and Socioeconomic Characteristics, Health Behavior and Morbidity in Cigarette Smokers Prior to Quitting Compared to Persistent Smokers and Non-Smokers," Journal of Clinical Epidemiology 41(2): 139-150, 1988.

Friedman, G.D., Siegelau, A.B., Dales, L.G. and Seltzer, C.C., "Characteristics Predictive of Coronary Heart Disease in Ex-Smokers Before They Stopped Smoking: Comparison with Persistent Smokers and Nonsmokers," Journal of Chronic Diseases 32(112): 175-190, 1979.

Friedman, G.D., Petitti, D.B., Bawol, R.D. and Siegelau, A.B., "Mortality in Cigarette Smokers and Quitters," New England Journal of Medicine 304(23): 1407-1410, 1981.

4. Seltzer, C.C., "Smoking and Coronary Heart Disease: What Are We to Believe?" American Heart Journal 100(3): 275-280, 1980.

CLAIM: The statistical evidence is so overwhelming that the inescapable conclusion is that smoking causes CHD.

RESPONSE:

-- Even if the statistical (epidemiological or population) literature were consistent, such data, by their very nature, do not prove cause-and-effect. That is because, among other reasons, statistical data do not provide information on any possible biological -- i.e., causal -- process. Even reports of the United States Surgeon General have recognized this. The first such report, in 1964, noted that "statistical methods cannot establish proof of a causal relationship in an association."¹ Similarly, in the context of discussing smoking and cardiovascular disease, the 1979 report noted that "correlation is not synonymous with causation."²

-- There are many inconsistencies in the statistical studies of smoking and CHD. In fact, some research has even failed to observe a statistical relationship.³ This has been particularly the case in studies of heart disease in women.⁴

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-- Perhaps the most well-known epidemiological study of heart disease risk factors is the Framingham Heart Study in the United States. Interestingly, on the basis of apparent differences between men and women in any CHD/smoking association, and on other inconsistencies in the data, a Harvard University researcher has suggested that the results from this study generally are "inconsistent" with the U.S. Surgeon General's views about cigarette smoking and CHD.⁵

-- It is also a statistical paradox that trends in CHD rates over time do not correspond closely with trends in cigarette smoking. In recent decades, for example, trends in CHD rates have been reported to be increasing in some countries and decreasing in others, but such trends have not been shown to be explained by changes in smoking.⁶

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REFERENCES

1. U.S. Department of Health, Education, and Welfare, Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service. Publication No. (PHS) 1103, Washington, D.C., U.S. Government Printing Office, (at 20), 1964.
 2. U.S. Department of Health, Education, and Welfare, Smoking and Health: A Report of the Surgeon General. Publication No. (PHS) DHEW 79-50066, Washington, D.C., U.S. Government Printing Office, (at 4-65), 1979.
 3. Cullen, K., Stenhouse, N.S., Wearne, K.L. and Welborn, T.A., "Multiple Regression Analysis of Risk Factors for Cardiovascular Disease and Cancer Mortality in Busselton, Western Australia -- 13-Year Study," J. Chron. Dis. 36(5): 371-377, 1983.
 4. Lapidus, L., Bengtsson, C., Lindquist, O., Sigurdsson, J.A. and Rafnsson, V., "Smoking -- A Risk Factor for Cardiovascular Disease in Women?" Scand. J. Prim. Health Care 4(4): 219-224, 1986.
- Kannel, W.B., "Update on the Role of Cigarette Smoking in Coronary Artery Disease," American Heart Journal 101(3): 319-328, 1981.
5. Seltzer, C.C., "Framingham Study Data and 'Established Wisdom' About Cigarette Smoking and Coronary Heart Disease," J. Clin. Epidemiol. 42(8): 743-750 (at 743), 1989.
 6. Heller, R.F., "The Declining Mortality from CHD," Journal of the Royal College of Physicians of London 17(1): 73, 1983.
- Welin, L., Wilhelmsen, L., Svärdsudd, K., Larsson, B. and Tibblin, G., "Increasing Mortality from Coronary Heart Disease among Males in Sweden," Cardiology 72(1/2): 75-80, 1985.

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**ENVIRONMENTAL TOBACCO SMOKE
EXPOSURE STUDIES
A REVIEW OF THE LITERATURE**

ETS: A CHARACTERIZATION

- Environmental tobacco smoke (ETS) is an aged and dilute mixture of sidestream smoke (SS), or the smoke from the burning end of the cigarette, and exhaled mainstream smoke (MS), the smoke to which the smoker is exposed.
- ETS differs chemically and physically from both MS and SS. ETS is a dynamic, ever-changing mixture which, as it ages and dissipates, undergoes chemical reactions and physical change. There is no single definable, reproducibly characterizable entity known as ETS.
- Dissipative forces such as air currents and attraction to surfaces influence SS and exhaled MS. Studies indicate that constituents in ETS are hundreds to thousands of times more dilute than either SS or MS. Often, concentrations of ETS constituents fall below detection limits of current scientific measurement devices.
- As ETS ages, a number of physico-chemical changes take place. Matter evaporates from SS particles as they age to ETS. During the aging process, ETS particles coagulate and increase in size. Chemical compounds partition between the gas and

particle phase of the smoke. (For example, nicotine is found in the particle phase of MS; in fresh SS, most of the nicotine is in the gas phase.) Decay patterns for constituents of ETS vary over time and are dependent upon physical conditions in the environment.

• ETS is not equivalent to either MS or SS. Many studies and reviews employ sidestream/mainstream smoke comparisons, ostensibly to demonstrate the kind and quantity of constituents involved in exposure to ETS. But such comparisons are deceptive and misleading. As two tobacco smoke chemists reported in 1990:¹

Although ETS originates from sidestream and exhaled mainstream smoke, the great dilution and other changes which these smoke streams undergo as they form ETS make their properties significantly different from those of ETS. Thus, the sidestream/mainstream ratios quoted in Table 1 can be misleading if used out of context. The important question is not the ratio of sidestream/mainstream but rather what is the concentration of the constituent in the indoor environment and how does it compare to levels from sources other than ETS. Studies based solely on observations of fresh sidestream, or highly and unrealistically concentrated ETS, should take into account the possible differences between these smokes and ETS found in real-life situations.

- Even the 1986 Report of the Surgeon General on ETS and the 1986 NRC/NAS Report on ETS conceded:

Comparison of the relative concentrations of various components of SS and MS smoke provides limited insights concerning the toxicological potential of ETS in comparison with active smoking. As described above, SS characteristics, as measured in a chamber, do not represent those of ETS, as inhaled by the non-smoker under nonexperimental conditions.²

Similarly, the NAS Report concluded:

Because the physicochemical nature of ETS, MS, and SS differ, the extrapolation of health effects from studies of MS or of active smokers to nonsmokers exposed to ETS may not be appropriate³

REFERENCES

1. Baker, R. and C. Proctor, "The Origins and Properties of Environmental Tobacco Smoke," Env. Int. (16): 231-245, 1990.

See also:

Löfroth, G., et al., "Characterization of Environmental Tobacco Smoke," Env Sci Technol (23): 610-614, 1989.

Scherer, G., et al., "Importance of Exposure to Gaseous and Particulate Phase Components of Tobacco Smoke in Active and Passive Smokers," Occup. Env. Health (62): 459-466, 1990.

Nystrom, C., et al., "Assessing the Impact of Environmental Tobacco Smoke on Indoor Air Quality: Current Status," Proceedings of the ASHRAE Conference, IAQ '86, April 20-23, 1986, Atlanta, Georgia: 213-233, 1986.

Rawbone, R., "The Aging of Sidestream Tobacco Smoke Components in Ambient Environments," Indoor Air Quality, ed. H. Kasuga, Springer-Verlag, Berlin Heidelberg: 55-61, 1990.

Proctor, C. and H. Dymond, "The Measurement of ETS Through Adsorption/Desorption Procedures," Indoor Air Quality, ed. H. Kasuga, Springer-Verlag, Berlin Heidelberg: 82-89, 1990.

Piade, J., et al., "Assessment of ETS Impact on Office Air Quality," Indoor Air Quality, ed. H. Kasuga, Springer-Verlag, Berlin Heidelberg: 112-119, 1990.

2. U.S. Department of Health and Human Services, A Report of the Surgeon General, The Health Consequences of Involuntary Smoking: 23-25, 1986.
3. Committee on Passive Smoking, Board on Environmental Studies and Toxicology, National Research Council, Environmental Tobacco Smoke. Measuring Exposures and Assessing Health Effects, National Academy Press, Washington, D.C.: 7-9, 1986.

EXPOSURE TO ETS

Published studies indicate that nonsmoker exposure to ETS under normal, everyday conditions is minimal. For example, researchers report that there is little difference in ambient levels of carbon monoxide in smoking and nonsmoking areas of workplaces and public places and in homes with and without smokers.¹⁻⁶ Other studies indicate that ETS contributes less than half of the total particles in the air of a typical public place.^{*7-14} Nicotine is often used as a marker for ETS

- * A paper published in a 1980 issue of Science magazine, in which the authors reported the results of their efforts to measure particles or particulates in the air of smoking and nonsmoking areas, is often cited to support the claim that ETS is a major indoor pollutant. The authors, Repace and Lowrey, contend that the levels of particles they observed in the smoking areas were much higher than in the nonsmoking areas. However, their study results are inconsistent with many others. For example, the average particle count attributed to ETS in their study was from three to twenty times higher than the average levels reported in other studies of office buildings, restaurants and residences.

There are a number of explanations for the authors' apparent overestimation of ETS exposure. First, they selectively sampled environments such as meeting and game rooms, bars and sandwich shops which did not represent normal occupancy conditions and where particulate levels would likely be high regardless of the presence or absence of tobacco smoke. Second, through inappropriate testing methods, they incorrectly assumed all particles in the air arose from ETS. However, as several researchers have noted, ETS typically contributes about one-third of the overall particle levels in indoor spaces. Moreover, particles also are generated by people and their everyday routine activities such as movement and cooking. (Repace, J. and A. Lowrey, "Indoor Air Pollution, Tobacco Smoke and Public Health," Science 208: 464-472, 1980.)

exposures because it is unique to tobacco smoke. Typical measurements of nicotine range from an exposure equivalent of 1/100 to 1/1000 of one filter cigarette per hour ¹⁵⁻²² This means that a nonsmoker would have to spend from 100 to 1000 hours in an office, restaurant or public place in order to be exposed to the nicotine equivalent of a single cigarette.

- Studies which have examined ETS constituent levels of nitrosamines, nitrogen oxides and volatile organic compounds (such as benzene**) report minimal contributions to overall ambient air levels in homes, the workplace and public places.²³⁻³⁶

** Benzene exposure from ETS is negligible, despite reports to the contrary.³⁷⁻³⁸ "Automotive fuel is, by far, the largest, most pervasive source of benzene exposure. In 1989, the U.S. Department of Health and Human Services estimated that 1 billion pounds of benzene were released into the atmosphere from the refueling and operation of approximately 130 million motor vehicles in 1976 [NIEHS, 1989]. This translates into 7.8 pounds of benzene per vehicle per year. In contrast, a pack-per-day smoker would generate approximately 0.008 pounds of benzene per year, assuming that, at most, 0.5 mg of benzene is generated from one cigarette (MS plus SS) [Hoffmann, 1990]. Based on these estimates, an average person is potentially exposed to 1,000 times more ambient benzene from one automobile than from a smoker in a given year." [From: Response of RJR, The U.S. EPA: "ETS: A Guide to Workplace Smoking Policies," October 1, 1990.]

Questionnaire Reliability:

- All of the epidemiologic studies on the purported association between ETS exposure and disease in nonsmokers rely solely upon questionnaires about exposure, rather than upon actual exposure data.³⁹⁻⁴¹ Recent studies indicate that questionnaires are an unreliable and inaccurate measure of exposure. Questionnaire responses about exposure vary widely when compared with actual measurements of ETS constituents in the ambient air.⁴¹

ETS and Radon:

- A theory that suggests that concentrations of radon decay products increase in the presence of tobacco smoke, thus implying an increased risk of lung cancer for the nonsmoker, has been reported in the literature.⁴²⁻⁴⁴ The theory suggests that radon decay products attach to particles (including ETS) in the air, remain suspended, and are subsequently taken up in the lungs of nonsmokers.
- However, actual data indicate that this is not the case.⁴⁵⁻⁴⁸ It is the unattached, gaseous fraction of radon which determines the dose of radiation to the respiratory tract. According to these data, as dust or particulate levels

increase, the unattached fraction of radon daughters will decrease, thereby lowering the potential dose of radiation to the lungs.

12. Oldaker, G., et al., "Results From Surveys of Environmental Tobacco Smoke in Restaurants," Indoor Air Quality, ed. H. Kasuga, Springer-Verlag, Berlin Heidelberg: 99-104, 1990.
13. Spengler, J., "Harvard's Indoor Air Pollution Health Study," Indoor Air Quality, H. Kasuga (ed.), Springer-Verlag, Berlin Heidelberg: 241-248, 1990.
14. Quackenboss, J. and Lebowitz, M., "Indoor-Outdoor Relationships for Particulate Matter: Exposure Classifications and Health Effects," Environ. Int., 15: 353-360, 1989.
15. Hinds, W. and First, M., "Concentrations of Nicotine and Tobacco Smoke in Public Places," New Eng. J. Med. 292(16): 844-845, 1975.
16. Badre, R., et al., "Pollution Atmospherique par la Fumee de Tabac (Atmospheric Pollution by Smoking)," Ann. Pharm. Fr. 36(9-10): 443-452, 1978. Translation.
17. Jenkins, R., et al., "Development and Application of a Thermal Desorption-Based Method for the Determination of Nicotine in Indoor Environments," Indoor and Ambient Air Quality, eds. R. Perry and P. Kirk, London, Selper Ltd.: 557-566, 1988.
18. Muramatsu, M., et al., "Estimation of Personal Exposure to Tobacco Smoke with a Newly Developed Nicotine Personal Monitor," Environ. Res. 35: 218-227, 1984.
19. Muramatsu, M., et al., "Estimation of Personal Exposure to Ambient Nicotine in Daily Environment," Arch. Occup. Environ. Health 59: 545-550, 1987.
20. Thompson, C., et al., "A Thermal Desorption Method for the Determination of Nicotine in Indoor Environments," Envir. Sci. Tech. 23: 429-435, 1989.
21. Folliart, D., et al., "Passive Absorption of Nicotine in Airline Flight Attendants," New Eng. J. Med., 308(18): 1105, 1983.
22. Oldaker, G. and Conrad, F., "Estimation of the Effect of Environmental Tobacco Smoke on Air Quality Within Passenger Cabins of Commercial Aircraft," Envir. Sci. Tech. 21: 994-999, 1987.
23. Lehnert, G., "Conclusion: In the Realm of Speculation," Munch med Wschr, 124 (1982) Nr. 4.

24. Schievelbein, H., "Are There Really Important New Findings About Passive Smoking?," Oeff Gesundheitswes, 44(0): 454-56, 1982. Translation.
25. Stehlik, G., et al., "Concentration of Dimethylnitrosamine in the Air of Smoke-Filled Rooms," Ecotoxicol Environ Safety 6: 495-500, 1982.
26. Sega, K. and M. Fugas, "Nitrogen Dioxide Concentrations in Residences," Indoor and Ambient Air Quality, eds. R. Perry and P. Kirk, London, Selper Ltd.: 493-496, 1988.
27. Good, B., et al., "Effect of Cigarette Smoking on Residential NO₂ Levels," Environ Int 8: 167-175, 1982.
28. Shimizu, Y., et al., "Influence of Indoor Air Pollution on NO₂ Personal Exposure Levels of Schoolchildren," Present and Future of Indoor Air Quality, eds. C. Bieva, et al., Brussels, Elsevier: 337-345, 1989.
29. Hendel-Kramer, A., et al., "Regression Model for Indoor Concentrations of Combustion-Generated Gases," Present and Future of Indoor Air Quality, eds. C. Bieva, et al., Brussels, Elsevier: 315-320, 1989.
30. Bayer, C. and Black, M., "Thermal Desorption/Gas Chromatographic/Mass spectrometric Analysis of Volatile Organic Compounds in the Offices of Smokers and Nonsmokers," Biomed and Envir Mass Spect 14(8): 363-367, 1987.
31. Proctor, C., et al., "Measurements of Environmental Tobacco Smoke in an Air-Conditioned Office Building," Environ. Technol. Letters (10): 1003-1018, 1989.
32. Godish, T., "Formaldehyde Exposures from Tobacco Smoke: A Review," AJPH 79(8): 1044-1045, 1989.
33. Godish, T., "Residential Formaldehyde: Increased Exposure Levels Aggravate Adverse Health Effects," J. of Environ. Health 53(3): 34-35, 1990.
34. Adlkofer, F., et al., "Significance of Exposure to Benzene and Other Toxic Compounds Through Environmental Tobacco Smoke," J. Cancer Res. Clin. Oncol. (116): 591-598, 1990.
35. Hugod, C., et al., "Exposure of Passive Smokers to Tobacco Smoke Constituents," Int. Arch. Occup. Environ. Health (42): 21-29, 1978.

36. Proctor, C., et al., "Measurement of Environmental Tobacco Smoke in an Air-Conditioned Office Building," Present and Future of Indoor Air Quality, eds. C.J. Bieva, et al., Brussels, Elsevier: 169-172, 1989.
37. Hattemer-Frey, H., "Benzene: Environmental Partitioning and Human Exposure," Environ. Res., 53: 221-232, 1990.
38. Wallace, L., "Major Sources of Exposure to Benzene and Other Volatile Organic Chemicals," Risk Analysis, 10(1): 59-64, 1990.
39. Coultas, D., et al., "Questionnaire Assessment of Lifetime and Recent Exposure to Environmental Tobacco Smoke," Am J of Epi. 130(2): 338-347, 1989.
40. Coultas, D., et al., "Variability of Measures of Exposure to Environmental Tobacco Smoke in the Home," Am Rev Resp Dis 142: 602-606, 1990.
41. Coultas, D., et al., "A Personal Monitoring Study to Assess Workplace Exposure to Environmental Tobacco Smoke," American J. of Public Health 80(8): 988-990, 1990.
42. Bergman, H. and Axelson, O., "Passive Smoking and Indoor Radon Daughter Concentrations," Lancet: 1308-09, 1983.
43. Bergman, H., et al., "Indoor Radon Daughter Concentrations and Passive Smoking," Env. Int. (12): 17-19, 1986.
44. Moghissi, A. and M. Seiler, "Enhancement of Exposure to Radon Progeny as a Consequence of Passive Smoking," Env. Int. (15): 261-64, 1989.
45. Upfal, M., et al., "Indoor Radon and Lung Cancer in China," J. Nat. Cancer Inst.: 1722, 1989.
46. Stebbings, J. and J. Dignam, "Contamination of Individuals by Radon Daughters: A Preliminary Study," Archives of Environ. Health 43(2): 149-54, 1988.
47. Pritchard, J. and J. Strong, "The Influence of Environmental Tobacco Smoke on Radon Dosimetry," Indoor Air '90: The Fifth International Conference on Indoor Air Quality and Climate, Toronto, Canada, July/August 1990: 33-38.
48. McAughey, J., et al., "Risk Assessment of Exposure to Indoor Air Pollutants," Env. Int. (11): 295-302, 1990.

DETERMINATION OF DOSE: COTININE

- It has been reported that cotinine, a substance converted from nicotine by the body, can be used as a biological marker to measure nonsmoker exposure to ETS.¹⁻² While some reports suggest that cotinine is a reliable marker for total exposure to tobacco smoke, many others do not.³⁻¹² Researchers have reported that individuals metabolize nicotine in different ways at different times and that elimination rates for cotinine vary among individuals. In addition, recent research indicates that diet may contribute to levels of nicotine and cotinine found in the body, thereby interfering with ambient air exposure levels.¹³ Scientists have also noted that different methods of analysis may influence final recorded levels of cotinine.¹⁴ And finally, because cotinine is a metabolite of a gas-phase constituent of ETS, nicotine, cotinine levels do not represent exposures to other constituents of ETS.

- In conclusion, cotinine is not a reliable quantitative measure of ETS exposure. This is because body fluid levels of cotinine cannot be attributed solely to nicotine in ETS, and because body fluid levels of cotinine do not correlate well with actual ambient air exposures to ETS or with ETS constituents other than nicotine. At best, cotinine may be used as a qualitative marker of ambient nicotine exposures.

REFERENCES

1. Wald, N., et al., "Urinary Cotinine as Marker of Breathing Other People's Tobacco Smoke," Lancet I, 230-231, 1984.
2. Watts, R. et al., "Cotinine Analytical Workshop Report: Consideration of Analytical Methods for Determining Cotinine In Human Body Fluids as a Measure of Passive Exposure to Tobacco Smoke," Environ. Health Pers. 84: 173-182, 1990.
3. Curvall, M., et al., "Simulation and Evaluation of Nicotine Intake During Passive Smoking: Cotinine Measurements in Body Fluids of Nonsmokers Given Intravenous Infusions of Nicotine," Clin. Pharmacol. Ther. 47(1): 42-49, 1990.
4. Itani, S., et al., "A Comparison of Plasma and Urinary Nicotine and Cotinine Levels in Smokers and Nonsmokers: Nicotine Excretion Pathways are Possibly Differential According to the Dosage of Tobacco Smoke Uptake," Indoor Air Quality, ed. H. Kasuga, Springer-Verlag, Berlin Heidelberg: 202-212, 1990.
5. Idle, J., "Commentary: Titrating Exposure to Tobacco Smoke Using Cotinine -- A Minefield of Misunderstanding," J. Clin. Epidemiol. 43(4): 313-317, 1990.
6. Biber, A., et al., "Determination of Nicotine and Cotinine in Human Serum and Urine: An Interlaboratory Study," Toxicology Letters 35(1): 45-52, 1987.
7. Haley, N. et al., "Elimination of Cotinine from Body Fluids: Disposition in Smokers and Nonsmokers," AJPH 79(8): 1046-1048, 1989.
8. Cummings, K., et al., "Measurement of Current Exposure to Environmental Tobacco Smoke," Archives of Environ. Health 45(2): 74-79, 1990.
9. Lee, P., "Lung Cancer and Passive Smoking," Br. J. Cancer, 63: 161-162, 1991.
10. Johnson, L., et al., "Passive Smoking Under Controlled Conditions," Int. Arch. Occup. Environ. Health 56: 99-110, 1985.
11. Letzel, H., et al., "Measuring Problems in Estimating the Exposure to Passive Smoking Using the Excretion of Cotinine," Toxicology Letters 35(1): 35-44, 1987.

12. Schwartz, S., et al., "Mathematical Modelling of Nicotine and Cotinine as Biological Markers of Environmental Tobacco Smoke Exposure," Toxicology Letters 35(1): 53-58, 1987.
13. Castro, A. and N. Monji, "Dietary Nicotine and Its Significance in Studies on Tobacco Smoking," Bio Arch 2(2): 9197, 1986.
14. Adlkofer, F., et al., "Passive Smoking," N Engl J Med 312(11): 719-720, 1984.

DETERMINATION OF DOSE: LUNG RETENTION

- Cotinine is a biologically inactive substance which has not been correlated with ETS constituents retained in the lung. Several researchers have estimated levels of ETS particulate uptake by nonsmokers to approximate 0.02% (two-hundredth of one percent) that of the particulate exposure of an active smoker.¹⁻⁴

REFERENCES

1. Arundel, A., et al., "Never Smoker Lung Cancer Risks from Exposure to Particulate Tobacco Smoke," Environ Int 13: 409-426, 1987.
2. Adlkofer, F., "Biological Effects After Exposure to ETS," Indoor Air Quality: Symposium, Buenos Aires, National Academy of Sciences of Buenos Aires: 61-76, 1989.
3. McAughey, J., et al., "Respiratory Deposition of Environmental Tobacco Smoke," Indoor Air '90: The Fifth International Conference on Indoor Air Quality and Climate, Toronto, Canada, July/August: 361-366, 1990.
4. Comments of the R.J. Reynolds Tobacco Company on Appendix C to the EPA Draft Risk Assessment - Dosimetry of Environmental Tobacco Smoke, September 1990, B-1 - C-7.

DETERMINATION OF DOSE: MUTAGENS

- Some reports have suggested that the potential toxicity of ETS can be assessed by measuring mutagens in the body fluids of nonsmokers exposed to ETS.¹⁻³ Mutagens are substances capable of altering the genetic structure of cells. It is suggested that the presence of mutagens in body fluids (e.g. urine) may be an indication that an individual has been exposed to substances capable of inducing cancer.
- Impetus for the theory arises, in part, from studies which report that various constituents of ETS collected through airborne samples are capable of inducing mutations in bacteria.⁴⁻⁶
- However, the significance of such reported findings has not been established. Virtually all air samples, whether in the presence or absence of smoking, are mutagenic. Indeed, no substance, including food and natural materials, has been unequivocally shown to be free of carcinogenic and/or mutagenic properties. In addition, it has been reported that sidestream smoke exhibits diminished mutagenic activity as it ages and becomes diluted (i.e., as it becomes ETS).⁷

- With few exceptions, studies which have compared mutagens in the body fluids of nonsmokers exposed to realistic levels of ETS and nonsmokers not exposed to ETS report no significant difference in mutagenic activity.⁸⁻¹¹
- The few studies reporting significant increases in urinary mutagenicity among individuals exposed to ETS¹⁻³ did not employ realistic levels of exposure to ETS, and they did not control adequately for the presence of mutagens in the diet of the study subjects.

REFERENCES

1. Bos, R., et al., "Excretion of Mutagens in Human Urine After Passive Smoking," Cancer Letters (19): 85-90, 1983.
2. Husgafvel-Pursiainen, K., et al., "Passive Smoking at Work: Biochemical and Biological Measures of Exposure to Environmental Tobacco Smoke," Int. Arch. Occup. Environ. Health (59): 337-345, 1987.
3. Mohtashamipur, E., et al., "Urinary Excretion of Mutagens in Passive Smokers," Toxicol. Letters (35): 141-146, 1987.
4. Claxton, L., et al., "A Genotoxic Assessment of Environmental Tobacco Smoke Using Bacterial Bioassays," Mutation Res. (222): 81-99, 1989.
5. Lofroth, G., et al., "Public Exposure to Environmental Tobacco Smoke," Mutation Res. (202): 103-110, 1988.
6. Matsushita, H., et al., "Highly Sensitive Methods for the Evaluation of Carcinogens and Mutagens Indoor," Indoor Air Quality, ed. H. Kasuga, Springer-Verlag, Berlin Heidelberg: 371-382, 1990.
7. Sonnenfeld, G. and D. Wilson, "The Effect of Smoke Age and Dilution on the Cytotoxicity of Sidestream (Passive) Smoke," Toxicol. Letters (35): 89-94, 1987.
8. Scherer, G., et al., "Urinary Mutagenicity After Controlled Exposure to Environmental Tobacco Smoke (ETS)," Toxicology Letters 35(1): 135-140, 1987.
9. Bombick, D., et al., "Assessment of the Biological Activity of Mainstream or Environmental Tobacco Smoke (ETS) Using a Cellular Smoke Exposure Technique," Abstracts of the Twenty-Second Annual Scientific Meeting of the Environmental Mutagen Society, Kissimmee, Florida: April 1991.
10. Scherer, G., "Biomonitoring of Exposure to Potentially Genotoxic Substances from Environmental Tobacco Smoke," Environ. Int. (15): 49-56, 1989.
11. Scherer, G., "Quantitative and Qualitative Differences in Tobacco Smoke Uptake Between Active and Passive Smoking," Indoor and Ambient Air Quality, eds. R. Perry and P. Kirk, Selper Ltd., London: 189-194, 1988.

DOSE: OTHER BIOLOGICAL MARKERS

- It has been suggested that sidestream smoke (and by inference, ETS) contains polycyclic aromatic hydrocarbons (PAH), substances which have been designated as carcinogens by various governmental agencies. However, in a series of papers, German researchers report no significant differences in urinary PAH by-products among nonsmokers exposed to ETS and those not exposed.¹⁻³ Diet was reported to have a profound influence on PAH by-product formation in all study subjects.
- Japanese scientists have reported that individuals exposed to ETS have increased urinary levels of hydroxyproline (HOP), a substance believed to act as a marker for the breakdown of lung tissue.⁴ However, German researchers have reported no increase in HOP excretion among either smokers or nonsmokers exposed to ETS.⁵
- It has recently been suggested that DNA adducts can be utilized as biomarkers to assess exposure (dose) to ETS.⁶ (An adduct is a product derived from reactions between chemicals and biological material (such as DNA)). Research, however, does not conclusively support this theory; nonsmokers exposed to ETS do not appear to exhibit increased DNA adduct production.⁷ Other studies report no increased chromosomal changes in body

fluids of nonsmokers exposed to ETS.⁸⁻⁹

REFERENCES

1. Scherer, G., et al., "Urinary Mutagenicity, Hydroxy-Phenanthrene, and Thioether Excretion After Exposure to Environmental Tobacco Smoke," Indoor Air Quality, ed. H. Kasuga, Springer-Verlag, Berlin Heidelberg: 138-146, 1990.
2. Martin, F., et al., "Urinary Excretion of Hydroxy-Phenanthrenes After Intake of Polycyclic Aromatic Hydrocarbons," Environ. Int. (15): 41-47, 1989.
3. Hoepfner, H., et al., "Hydroxy-Phenanthrenes in the Urine of Non-Smokers and Smokers," Toxicology Letters (35): 67-71, 1987.
4. Kasuga, H., "An Introduction to the Study of Smoking Using Urinary Hydroxyproline," Indoor Air Quality, ed. H. Kasuga, Springer-Verlag, Berlin Heidelberg: 37-52, 1990.
5. Adlkofer, F., "The Significance of Urinary Hydroxyproline Excretion in Smokers and Passive Smokers," Indoor Air Quality, ed. H. Kasuga, Springer-Verlag, Berlin Heidelberg: 213-218, 1990.
6. Perera, F., et al., "DNA Adducts, Protein Adducts, and Sister Chromatid Exchange in Cigarette Smokers and Nonsmokers," JNCI 79(3): 449-456, 1987.
7. Holz, O., et al., "³²P-postlabelling Analysis of DNA Adducts in Monocytes of Smokers and Passive Smokers," Int. Arch. Occup. Environ. Health, 62: 299-303, 1990.
8. Sorsa, M., et al., "Cytogenetic Effects of Tobacco Smoke Exposure Among Involuntary Smokers," Mutation Res. 222(2): 111-116, 1989.
9. Husgafvel-Pursiainen, K., "Sister-Chromatid Exchange and Cell Proliferation in Cultured Lymphocytes of Passively and Actively Smoking Restaurant Personnel," Mutation Res. 190: 211-215, 1987.

BIOLOGICAL PLAUSIBILITY

- The argument for the biological plausibility of the role of ETS in disease causation depends upon the simplistic claim that since mainstream (MS) and sidestream (SS) smoke contain carcinogenic substances, so must ETS. However, this analogy is not proved.
- ETS has never been shown to be carcinogenic in any animal species. Only two animal inhalation experiments investigating ETS and lung cancer have been published. Both studies report no meaningful histopathological differences between animals exposed to ETS and those which were not exposed. In a study conducted by the American Health Foundation,³ the investigators exposed one group of hamsters to mainstream smoke and another group to ETS. Animals exposed to mainstream smoke and ETS lived longer than the sham treated controls. The investigators reported that overall there was no marked increase in tumor incidence in animals exposed to either mainstream smoke or ETS after 18 months of exposure. The second study was a 90-day ETS inhalation study of rats and hamsters.⁴ Animals were exposed to ETS concentrations 100 times those concentrations encountered by nonsmokers. These researchers reported no histopathological differences between exposed and control animals. Electron microscopy revealed

pulmonary changes which could be expected to occur under similar exposure conditions with other substances.

- In addition, recent reviews of the literature on suspected pulmonary carcinogens have indicated that none of the individual constituents in sidestream smoke classified as potentially carcinogenic has been found to induce pulmonary cancer via inhalation in experimental animals.⁵⁻⁶
- ETS has not be shown to be mutagenic in any animal or cell culture system when tested at realistic levels of exposure (See Section III).
- These points undermine the credibility of the argument for the biological plausibility of ETS in disease causation.

REFERENCES

1. Haley, N., et al., "Uptake of Sidestream Smoke by Syrian Golden Hamsters," Toxicol. Letters 35 (1987): 83-88.
2. Haley, N., "Sidestream Smoke Uptake By Syrian Golden Hamsters in An Inhalation Bioassay," Indoor Air '87: Proceedings of the 4th International Conference on Indoor Air Quality and Climate, Institute for Water, Soil and Air Hygiene, Berlin: 68-73, 1987.
3. American Health Foundation, "Experimental Tobacco Carcinogenesis," Application for Continuation Grant to Department of Health and Human Services, U.S. Public Health Service, May 1988.
4. Adlkofer, F., et al., "Exposure of Hamsters and Rats to Sidestream Smoke of Cigarettes: Preliminary Results of a 90-Day-Inhalation Study," Indoor and Ambient Air Quality, eds. R. Perry and P. Kirk, London, Selper Ltd.: 252-258, 1988.
5. Aviado, D., "Suspected Pulmonary Carcinogens in Environmental Tobacco Smoke," Environ. Tech. Letters, 9: 539-544, 1988.
6. Aviado, D., "Health Effects of 50 Selected Constituents of Environmental Tobacco Smoke," Indoor Air Quality, ed. H. Kasuga, Springer-Verlag, Berlin Heidelberg: 383-389, 1990.

**ETS AND
LUNG CANCER IN NONSMOKERS**

VOLUME I

2025500427

PRIMARY EPIDEMIOLOGIC STUDIES ON ETS AND LUNG CANCER

Introduction

Currently, 29 epidemiologic studies examining lung cancer incidence and spousal smoking have been published.¹⁻²⁹ Tables 1, 2 and 3 list the United States, Asian and European studies, respectively. For purposes of comparison, the relative risks (point estimates) given in the tables are the overall point estimates for spousal smoking reported in the papers. In some cases, the risk in the table was selected from numerous point estimates presented in the paper, based on different definitions of exposure, breakdown of the sample by histological type, etc.

Brief synopses and copies of the papers associated with these studies follow this introduction, at Tabs 1 to 29, arranged in chronological order. The copies are highlighted in yellow for useful information and in blue for negative statements.

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United States Studies

Ten of these studies on spousal smoking and lung cancer in nonsmokers (one cohort, nine case-control) were conducted in the United States (Table 1).^{3,5,7-9,11,14,16,24,25} None of the relative risks (RR) for spousal smoking reported in these studies is statistically significant. The most recently published paper, that by Janerich, et al., is based upon an unpublished dissertation by Luis Varela.²⁴ The Janerich, et al., paper discusses a subset of Varela's case-control study, and reports no statistically significant increased risk for spousal smoking, workplace exposure, or exposure in social settings. (It does, however, report a statistically significant increased risk for exposure during childhood (see below).) Overall, the Varela study is important because of its large size and appropriate study design.

Table 1. United States Studies of Spousal Smoking in Women

<u>Study</u>	<u>Risk Estimate(s)</u>	<u>Comment</u>
Garfinkel, 1981	1.27 (95% CI 0.85-1.89) 1.10 (95% CI 0.77-1.61)	Large cohort study; results contrast with Hirayama
Correa, et al., 1983	2.07 (no CI; n.s.)	Extremely small sample size
Buffler, et al., 1984	0.78 (95% CI 0.34-1.81)	
Kabat and Wynder, 1984	not given	No significant differences between cases and controls regarding ETS exposure at home
Garfinkel, et al., 1985	1.23 (95% CI 0.94-1.60)	Numerous odds ratios presented
Wu, et al., 1985	1.2 (95% CI 0.5-3.3)	Adenocarcinoma only
Brownson, et al., 1987	1.68 (95% CI 0.39-2.97)	Hours per day as exposure category; adenocarcinoma only
Humble, et al., 1987	1.8 (95% CI 0.6-5.4)	
Varela, 1987	numerous	No statistically significant point estimate was presented in 73 different measures of spousal smoking
Janerich, et al., 1990	0.93 (95% CI 0.55-1.57)	Published data for subset of Varela, 1987
Kabat, 1990	0.90 (95% CI 0.46-1.76)	Study in progress; surrogate is "exposed in adulthood at home"

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Asian Studies

In contrast, 13 epidemiologic studies on spousal smoking and lung cancer in nonsmokers (one cohort, twelve case-control) have been conducted in China and Japan (hereafter, "Asian studies") (Table 2).^{1,4,10,12,15,17,18,20-22,27,28,29} Of this group, several studies report statistically significant relative risks. However, none of the reported relative risks is greater than 2.5; relative risks under 3.0 have been described as "weak" (see Criticisms section in this notebook). Of particular interest is the 1990 paper by Wu-Williams, et al., conducted in northeastern China.²⁸ This paper reports a statistically significant negative risk associated with ETS exposure. Other factors (particularly indoor air quality) were reported to be associated with an elevated risk of lung cancer in the Wu-Williams, et al., study; such confounders were not always accounted for in the other Asian studies (see section on Confounders in this notebook).

Table 2. Asian Studies of Spousal Smoking in Women

<u>Study</u>	<u>Point Estimate(s)</u>	<u>Comment</u>
Hirayama, 1981	2.08 (no CI)	Large cohort study; heavily criticized for improper age-standardization and other flaws
Hirayama, 1984	1.45 (90% CI 1.04-2.02)	Further report on above study
Chan and Fung, 1982	not given	Negative association; suggests more "passive smokers" among controls than cases
Lam, W.K., 1985	not given	Unpublished dissertation; suggests that spousal smoking may be associated with peripheral adenocarcinoma
Akiba, et al., 1986	1.5 (90% CI 1.0-2.5)	Study of atom bomb survivors
Gao, et al., 1987	0.9 (95% CI 0.6-1.4)	"Overall exposure" as surrogate
Koo, et al., 1987	1.64 (95% CI 0.87-3.09)	
Lam, T.H., et al., 1987	1.65 (95% CI 1.16-2.35)	
Geng, et al., 1988	2.16 (95% CI 1.03-4.53)	
Inoue and Hirayama, 1988	2.25 (95% CI 0.91-7.10)	Very small sample size
Shimizu, et al., 1988	1.1 (no CI; n.s.)	Reported statistically significant elevated risks for smoking by case's mother or case's husband's father

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<u>Study</u>	<u>Point Estimate(s)</u>	<u>Comment</u>
Sobue, et al., 1990	0.94 (95% CI 0.62-1.40)	
Wu-Williams, et al., 1990	0.7 (95% CI 0.6-0.9)	Point estimate is statistically significantly negative
Liu, et al., 1991	0.77 (95% CI 0.30-1.96)	Presence of at least one smoker in household used as surrogate

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European Studies

Six studies on spousal smoking and nonsmoker lung cancer were conducted in Europe (Table 3).^{2,7,13,19,23,26} Statistical significance was reported in two studies, both by the same research group.^{2,26} No major cohort study has yet been conducted in Europe. The cohort studied by Gillis, et al., and Hole, et al., although large, has few lung cancer deaths.⁷

Table 3. European Studies of Spousal Smoking in Women

<u>Study</u>	<u>Risk Estimate</u>	<u>Comment</u>
Trichopoulos, et al., 1981	2.4 (no CI)	Greece; small case-control study; has been heavily criticized
Trichopoulos, et al., 1983	2.4 (no CI) 3.4 (no CI)	Additional cases and controls added since first paper
Gillis, et al., 1984	not given	Scotland; cohort study; very few lung cancer death (4 cases, 4 controls in women)
Hole, et al., 1989	2.41 (95% CI 0.45-12.83)	Continuation of Gillis, et al., 1984
Lee, et al., 1986	1.00 (95% CI 0.37-2.71)	England
Pershagen, et al., 1987	1.2 (95% CI 0.7-2.1)	Sweden
Svensson, et al., 1989	1.2 (95% CI 0.4-2.9)	Sweden; surrogate is "exposure as adult at home or at work"
Kalandidi, et al., 1990	1.92 (95% CI 1.02-3.59)	Greece; related to Trichopoulos study

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Childhood Exposure to ETS and Adult Lung Cancer in Nonsmokers

When the Janerich, et al., paper was published in 1990, the media focused on a single statistically significant risk ratio (OR) reported by the authors, i.e., an estimated OR of 2.07 (95% CI 1.16-3.68) for "household exposure to 25 or more smoker-years during childhood and adolescence."²⁴ This OR is the only statistically significant estimate out of 13 exposure categories in the paper. A single statistically significant point estimate could have easily occurred by chance alone in a set of analyses this large.

Only a few other studies have included questions concerning exposure to ETS during childhood, i.e., parental smoking. 5,9,11,12,15,23,25,27 Regarding these studies, Ernst Wynder and Geoffrey Kabat wrote in a 1990 publication:

No consistent association has been reported for lung cancer and exposure to ETS in childhood, which might be expected to exert a greater effect, especially when followed by exposure throughout adulthood. Of course, recall of ETS exposure in childhood is more difficult than recall of such exposure in adulthood.

(Wynder, E.L. and Kabat, G.C., "Environmental Tobacco Smoke and Lung Cancer: A Critical Assessment," Indoor Air Quality, ed. H. Kasuga (Berlin, Heidelberg: Springer-Verlag, 1990): 5-15.)

Table 4 presents the reported risk estimates from the studies (9 to-date) which discuss childhood ETS exposure and lung

cancer in nonsmokers. The studies are arranged chronologically in the table. The abbreviation "n.s." stands for "not significant."

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Table 4. Childhood Exposure to ETS and Adult Nonsmoker Lung Cancer Risk

<u>Study</u>	<u>Point Estimate</u>	<u>Statistical Significance</u>
Correa, et al., 1983	not given	n.s.
Garfinkel, et al., 1985 females	0.91 (95% CI 0.74-1.12)	n.s.
Wu, et al., 1985 females	0.6 (95% CI 0.2-1.7)	n.s.
Akiba, et al., 1986	not given	n.s.
Gao, et al., 1987 females	1.1 (95% CI 0.7-1.7)	n.s.
Svensson, et al., 1989 females, father's smoking	0.9 (95% CI 0.4-2.3)	n.s.
females, mother's smoking	3.3 (95% CI 0.5-18.8)	n.s.
Janerich, et al., 1990 1-24 smoker/yr exposure	1.09 (95% CI 0.68-1.73)	n.s.
≥ 25 smoker/yr exposure	2.07 (95% CI 1.16-3.68)	significantly positive
Kabat, et al., 1990 males	0.73 (95% CI 0.34-1.59)	n.s.
females	1.68 (95% CI 0.86-3.27)	n.s.
Sobue, et al., 1990 father's smoking	0.60 (95% CI 0.40-0.91)	significantly negative
mother's smoking	1.71 (95% CI 0.95-3.10)	n.s.
other household members	1.13 (95% CI 0.69-1.87)	n.s.

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Exposure to ETS in the Workplace and Lung Cancer in Nonsmokers

The issue of ETS in the workplace is currently a focus of public interest, as evidenced by the 1990 draft Guide to Workplace Smoking Policies prepared by the United States Environmental Protection Agency. This document is based on the EPA's draft risk assessment, which used data from epidemiologic studies which assessed ETS exposure in terms of spousal smoking, not smoking in the workplace.

The current epidemiologic data on workplace exposures to ETS and lung cancer in nonsmokers are reported in eleven studies which examined workplace exposure via questionnaire.^{8,9,11,13,17,22-26,28} None of these studies provides adequate support for an increased risk of lung cancer associated with ETS exposure in the workplace. Only one study reports a single marginally statistically significant risk. The point estimates of the studies (in chronological order) are presented in Table 5. (In the table, "n.s." stands for "not significant.")

Table 5. Exposure to ETS in the Workplace and Lung Cancer Risk in Nonsmokers

<u>Study</u>	<u>Point Estimate</u>	<u>Statistical Significance</u>
Kabat and Wynder, 1984		
males	18/25 cases vs. 11/25 controls	marginally significant
females	26/53 cases vs. 31/53 controls	n.s.
Garfinkel, et al., 1985		
females, 5 yr exposure	0.88 (95% CI 0.66-1.18)	n.s.
females, 25 yr exposure	0.93 (95% CI 0.73-1.18)	n.s.
Wu, et al., 1985		
females	1.3 (95% CI 0.5-3.3)	n.s.
Lee, et al., 1986	several indices	all n.s.
Koo, et al., 1987		
females	several ORs	all n.s.
Shimizu, et al., 1988		
females	1.2 (no CI given)	n.s.
Svensson, et al., 1989		
females, at home <u>or</u> at work	1.2 (95% CI 0.4-2.9)	n.s.
females, at home <u>and</u> at work	2.1 (95% CI 0.6-8.1)	n.s.
Janerich, et al., 1990		
150 person/yr exposure	0.91 (95% CI 0.80-1.09)	n.s.
Varela, 1987	27 analyses	all n.s.
Kabat, 1990		
males	0.98 (95% CI 0.46-2.10)	n.s.
females	1.00 (95% CI 0.49-2.06)	n.s.

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<u>Study</u>	<u>Point Estimate</u>	<u>Statistical Significance</u>
Kalandidi, et al., 1990 females	1.08 (95% CI 0.24-4.87)	n.s.
Wu-Williams, et al., 1990 females	1.1 (95% CI 0.9-1.6)	n.s.

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REFERENCES

1. Hirayama, T., "Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung Cancer: A Study from Japan," British Medical Journal I, 282: 183-185, 1981.

Hirayama, T., "Cancer Mortality in Nonsmoking Women with Smoking Husbands Based on a Large-Scale Cohort Study in Japan," Preventive Medicine 13: 680-690, 1984.

Hirayama, T., "Lung Cancer in Japan: Effects of Nutrition and Passive Smoking," Lung Cancer: Causes and Prevention, eds. M. Mizell and P. Correa (New York: Verlag Chemie International, 1984): 175-195.
2. Trichopoulos, D., Kalandidi, A., Sparros, L. and MacMahon, B., "Lung Cancer and Passive Smoking," International Journal of Cancer 27(1): 1-4, 1981.

Trichopoulos, D., Kalandidi, A. and Sparros, L., "Lung Cancer and Passive Smoking: Conclusions of Greek Study," The Lancet II: 677-678, 1983.
3. Garfinkel, L., "Time Trends in Lung Cancer Mortality Among Nonsmokers and a Note on Passive Smoking," Journal of the National Cancer Institute 66: 1061-1066, 1981.
4. Chan, W.C. and Fung, S.C., "Lung Cancer in Non-Smokers in Hong Kong," Cancer Campaign Vol. 6, Cancer Epidemiology, ed. E. Grundmann (Stuttgart: Gustav Fischer Verlag, 1982): 199-202.
5. Correa, P., Pickle, L.W., Fontham, E., Lin, Y. and Haenszel, W., "Passive Smoking and Lung Cancer," The Lancet II: 595-597, 1983.
6. Buffler, P.A., Pickle, L.W., Mason, T.J. and Contant, C., "The Causes of Lung Cancer in Texas," Lung Cancer: Causes and Prevention, eds. M. Mizell and P. Correa (New York: Verlag Chemie International, 1984): 83-99.
7. Gillis, C.R., Hole, D.J., Hawthorne, V.M. and Boyle, P., "The Effect of Environmental Tobacco Smoke in Two Urban Communities in the West of Scotland," ETS - Environmental Tobacco Smoke: Report from a Workshop on Effects and Exposure Levels, eds. R. Rylander, Y. Peterson and M.-C. Snella, European Journal of Respiratory Diseases, Supplement 133(65): 121-126, 1984.

Hole, D.J., Gillis, C.R., Chopra, C. and Hawthorne, V.M., "Passive Smoking and Cardiorespiratory Health in a General

- Population in the West of Scotland," British Medical Journal 299: 423-427.
8. Kabat, G. and E. Wynder, "Lung Cancer in Nonsmokers," Cancer 53: 1214-1221, 1984.
 9. Garfinkel, L., Auerbach, O. and Joubert, L., "Involuntary Smoking and Lung Cancer: A Case-Control Study," Journal of the National Cancer Institute 75(3): 463-469, 1985.
 10. Lam, W.K., A Clinical and Epidemiological Study of Carcinoma of Lung in Hong Kong, M.D. thesis submitted to University of Hong Kong, 1985 (only some pages available).
 11. Wu, A., Henderson, B.E., Pike, M.C. and Yu, M.C., "Smoking and Other Risk Factors for Lung Cancer in Women," Journal of the National Cancer Institute 74(4): 747-751, 1985.
 12. Akiba, S., Kato, H. and Blot, W.J., "Passive Smoking and Lung Cancer Among Japanese Women," Cancer Research 46: 4804-4807, 1986.
 13. Lee, P., Chamberlain, J. and Alderson, M.R., "Relationship of Passive Smoking to Risk of Lung Cancer and Other Smoking-Associated Diseases," British Journal of Cancer 54: 97-105, 1986.
 14. Brownson, R.C., Reif, J.S., Keefe, T.J., Ferguson, S.W. and Pritzl, J.A., "Risk Factors for Adenocarcinoma of the Lung," American Journal of Epidemiology 125(1): 25-34, 1987.
 15. Gao, Y.-T., Blot, W.J., Zheng, W., Ershow, A.G., Hsu, C.W., Levin, L.I., Zhang, R. and Fraumeni, J.F., "Lung Cancer Among Chinese Women," International Journal of Cancer 40: 604-609, 1987.
 16. Humble, C.G., Samet, J.M. and Pathak, D.R., "Marriage to a Smoker and Lung Cancer Risk," American Journal of Public Health 77(5): 598-602, 1987.
 17. Koo, L., Ho, J.H.-C., Saw, D. and Ho, C.-Y., "Measurements of Passive Smoking and Estimates of Lung Cancer Risk Among Non-Smoking Chinese Females," International Journal of Cancer 39: 162-169, 1987.
 18. Lam, T.H., Kung, I.T.M., Wong, C.M., Lam, W.K., Kleeven, J.W.L., Saw, D., Hsu, C., Seneviratne, S., Lam, S.Y., Lo, K.K. and Chan, W.C., "Smoking, Passive Smoking and Histological Types in Lung Cancer in Hong Kong Chinese Women," British Journal of Cancer 56(5): 673-678, 1987.

19. Pershagen, G., Hrubec, Z. and Svensson, C., "Passive Smoking and Lung Cancer in Swedish Women," American Journal of Epidemiology 125(1): 17-24, 1987.
20. Geng, G.-Y., Liang, Z.H., Zhang, A.Y. and Wu, G.L., "On the Relationship Between Smoking and Female Lung Cancer," Smoking and Health 1987, eds. M. Aoki, S. Hisamichi and S. Tominaga (Amsterdam: Excerpta Medica, 1988): 483-486.
21. Inoue, R. and Hirayama, T., "Passive Smoking and Lung Cancer in Women" Smoking and Health 1987, eds. M. Aoki, S. Hisamichi and S. Tominaga (Amsterdam: Excerpta Medica, 1988): 283-285.
22. Shimizu, H., Morishita, M., Mizuno, K., Masuda, T., Ogura, Y., Santo, M., Nishimura, M., Kunishima, K., Karasawa, K., Nishiwaki, K., Yamamoto, M., Hisamichi, S. and Tominaga, S., "A Case-Control Study of Lung Cancer in Nonsmoking Women," Tohoku Journal of Experimental Medicine 154: 389-397, 1988.
23. Svensson, C., Pershagen, G. and Klominek, J., "Smoking and Passive Smoking in Relation to Lung Cancer in Women," Acta Oncologica 28(5): 623-629, 1989.
24. Janerich, D., Thompson, W.D., Varela, L.R., Greenwald, P., Chorost, S., Tucci, C., Zaman, M.B., Melamed, M.R., Kiely, M. and McKneally, M.F., "Lung Cancer and Exposure to Tobacco Smoke in the Household," The New England Journal of Medicine 323: 632-636, 1990.

Varela, L., "Assessment of the Association Between Passive Smoking and Lung Cancer," dissertation submitted to Yale University, 1987.
25. Kabat, G.C., "Epidemiologic Studies of the Relationship Between Passive Smoking and Lung Cancer," Toxicology Forum, 1990 Annual Winter Meeting (transcript): 187-199, 1990.
26. Kalandidi, A., Katsouyanni, K., Voropoulou, N., Bastas, G., Saracci, R. and Trichopoulos, D., "Passive Smoking and Diet in the Etiology of Lung Cancer Among Non-Smokers," Cancer Causes and Control 1: 15-21, 1990.
27. Sobue, T., Suzuki, R., Nakayama, N., Inubuse, C., Matsuda, M., Doi, O., Mori, T., Furuse, K., Fukuoka, M., Yasumitsu, T., Kuwabara, O., Ichigaya, M., Kurata, M., Kuwabara, M., Nakahara, K., Endo, S. and Hattori, S., "Passive Smoking Among Nonsmoking Women and the Relationship Between Indoor Air Pollution and Lung Cancer Incidence -- Results of a Multicenter

Case Controlled Study," Gan to Rinsho 36(3): 329-333, 1990 (translation).

28. Wu-Williams, A.H., Dai, X.D., Blot, W., Xu, Z.Y., Sun, X.W., Xiao, H.P., Stone, B.J., Yu, S.F., Feng, Y.P., Ershow, A.G., Sun, J., Fraumeni, J.F. and Henderson, B.E., "Lung Cancer Among Women in North-East China," British Journal of Cancer 62: 982-987, 1990.
29. Liu, Z., He, X. and Chapman, R.S., "Smoking and Other Risk Factors for Lung Cancer in Xuanwei, China," International Journal of Epidemiology 20(1): 26-31, 1991.

OTHER STUDIES DISCUSSING LUNG CANCER

In addition to the primary lung cancer studies discussed in Section A of this notebook, there are several other studies which are sometimes mentioned in the context of epidemiologic studies on ETS and lung cancer. Because these studies are methodologically flawed or report incomplete data, they are of limited usefulness. For instance, the earlier studies (e.g., Knoth, et al., 1983; Miller, 1984; Sandler, et al., 1985) were excluded from the Letzel and Überla meta-analysis (1990), and even from the meta-analyses conducted by the National Academy of Sciences in 1986 and by the Environmental Protection Agency in 1990.

Following are brief summaries of each of these studies, focusing on their problems. Copies of these studies follow this introduction, arranged in chronological order and highlighted in yellow for useful information and in blue for adverse information.

Knoth, et al., 1983.

- This German study included a total of 792 lung cancer patients. There was no control population for comparison, and thus, the authors' conclusions are of limited value.¹
- One reviewer commented that this report contained "only tentative conclusions based on poor data analyzed by

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unacceptable methods."²

Sandler, et al., 1985

- Although the papers published by Sandler, et al., in 1985 focused on overall mortality, some numbers of lung cancer deaths were presented.³
- The methodology and interpretation of these studies have been heavily criticized (e.g., one scientist described the studies as "heavily flawed").⁴ The data presented are of limited value.

Dalager, et al., 1986.

- Data from three case-control studies conducted in the United States under the auspices of the National Cancer Institute were combined and analyzed in this study.⁵ (Two of the studies, Correa, et al., and Buffler, et al., were discussed in Section A of this notebook.)
- Because the Dalager paper includes two primary studies on ETS and lung cancer, if it were included in considerations of the epidemiologic studies, it would result in some data being "counted" twice.

Lloyd, et al., 1986..

- In a study investigating the high rate of lung cancer in one town in Scotland, relatives of 42 cases who had died of lung cancer and of 42 matched controls who had died of other causes were interviewed.⁶
- Conclusions about ETS exposure were based on smokers and nonsmokers combined, thus precluding comparisons to the primary studies cited in Section A of this notebook. However, the authors reported no statistically significant differences between cases and controls for any questions relative to personal smoking or to ETS.

Katada, et al., 1988.

- This study, using hospitalized individuals in Nara, Japan, included only 25 female lung cancer cases (some of whom were smokers) and 50 female controls.⁷
- All of the cases reported present exposure to ETS, all but two reported past exposure, and all but four reported childhood exposure. Thus, the reference categories (i.e., non-exposed women) are too small to allow appropriate calculations of relative risk.

- Nevertheless, none of the case-control comparisons was statistically significant at the 5% level. (Note: the paper also bases some of its conclusions on nonsmokers and smokers combined.)

Lam and Cheng, 1988

- This paper reviews four lung cancer studies previously conducted in Hong Kong, all of which are presented in the Primary Studies section of this notebook.⁸
- Using meta-analysis, Lam and Cheng calculate a statistically significant summary point estimate for the four studies.

Chen, et al., 1990

- In 1990, conclusions based on a study of 332 cases and 635 group-matched hospital controls in Taiwan were published.⁹
- For ETS exposure, point estimates achieving statistical significance were reported; however, it appears that these point estimates were calculated using both nonsmokers and active smokers, and are thus not comparable with other studies of nonsmokers only.

Miller, 1990.

- Miller used newspaper death notices to ascertain cancer deaths in women in northwestern Pennsylvania, and then interviewed surviving next-of-kin to obtain information on the deceased women. This approach could be expected to result in problems related to accurate recall by those interviewed.¹⁰
- In a 1984 paper, Miller examined "all cancer deaths" (See Other Cancers section in this notebook); in the 1990 paper, he provides numbers of cancer deaths by site.

REFERENCES

1. Knoth, A., Bohn, H. and Schmidt, F., "Passive Smoking as a Causative Factor of Lung Cancer in Nonsmoking Women," Med Clin Prax 78(2): 56-59, 1983 (translation).
2. Heller, W., "Lung Cancer and Passive Smoking," Lancet II: 1309, 1983.
3. Sandler, D.P., Everson, R.B. and Wilcox, A.J., "Passive Smoking in Adulthood and Cancer Risk," American Journal of Epidemiology 121: 37-48, 1985.

Sandler, D.P., Everson, R.B., Wilcox, A.J. and Browder, J.P., "Cancer Risk in Adulthood from Early Life Exposure to Parents' Smoking," American Journal of Public Health 75(5): 487-492, 1985.

Sandler, D.P., Wilcox, A.J. and Everson, R.B., "Cumulative Effects of Lifetime Passive Smoking on Cancer Risk," Lancet II: 312-314, 1985.
4. Burch, P.R.J., "Lifetime Passive Smoking and Cancer Risk," Lancet II: 866, 1985.

Higgins, I., "Lifetime Passive Smoking and Cancer Risk," Lancet II: 866-867, 1985.

Lee, P.N., "Lifetime Passive Smoking and Cancer Risk," Lancet II: 1444, 1985.

Burch, P.R.J., "Passive Smoking in Adulthood and Cancer Risk," American Journal of Epidemiology 123 (2): 368-369, 1986.

Friedman, G., "Passive Smoking in Adulthood and Cancer Risk," American Journal of Epidemiology 123 (2): 367, 1986.

Mantel, N., "Passive Smoking in Adulthood and Cancer Risk," American Journal of Epidemiology 123 (2): 367-368, 1986.
5. Dalager, N.A., Pickle, L.W., Mason, T.J., Correa, P., Fontham, E., Stemhagen, A., Buffler, P.A., Ziegler, R.G. and Fraumeni, J.F., "The Relation of Passive Smoking to Lung Cancer," Cancer Research 46: 4808-4811, 1986.
6. Lloyd, O.L., Ireland, E., Tyrrell, H. and Williams, F., "Respiratory Cancer in a Scottish Industrial Community: A Retrospective Case-Control Study," Journal of the Society for Occupational Medicine 36(1): 2-8, 1986.

7. Katada, H., Mikami, R., Konishi, M., Koyama, Y. and Narita, N., "Effect of Passive Smoking in Lung Cancer Development in Women in the Nara Region," Gan No Rinsho 34(1): 21-27, 1988 (translation).
8. Lam, T.H. and Cheng, K.K., "Passive Smoking Is a Risk Factor for Lung Cancer in Never Smoking Women in Hong Kong," Smoking and Health 1987 eds. M. Aoki, S. Hisamichi and S. Tominaga (Amsterdam: Excerpta Medica, 1988): 279-281.
9. Chen, C.-J., Wu, H.-Y., Chuang, Y.-C., Chang, A.-S., Luh, K.-T., Chao, H.-H., Chen, K.-Y., Chen, S.-G., Lai, G.-M., Huang, H.-H. and Lee, H.-H., "Epidemiologic Characteristics and Multiple Risk Factors of Lung Cancer in Taiwan," Anticancer Research 10: 971-976, 1990.
10. Miller, G.H., "The Impact of Passive Smoking: Cancer Deaths Among Nonsmoking Women," Cancer Detection and Prevention 14(5): 497-503, 1990.

**ETS AND
LUNG CANCER IN NONSMOKERS**

VOLUME II

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CRITICISMS OF THE EPIDEMIOLOGIC STUDIES ON ETS AND LUNG CANCER

Some general criticisms are applicable to the majority of the epidemiologic studies on ETS and lung cancer.

Strength of the association

- Wynder and Kabat wrote in 1990:

An association is generally considered weak if the odds ratio is under 3.0 and particularly when it is under 2.0, as is the case in the relationship of ETS and lung cancer.¹

Such a weak association calls for special attention to possible sources of bias and confounding.

Exposure bias

- Spouses, next-of-kin or friends are sometimes asked to estimate the amount of ETS to which they think the subject was exposed. This may result in something called "exposure bias" or "exposure misclassification."²
- Exposure indices and risk estimates based on this type of information may be improper and incorrect.
- One example of this was reported in the Garfinkel, et al., study, published in 1985, which reported relative risks of 0.83 when the cases answered questions about ETS, 0.77 when

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the cases' husbands answered, and 3.57 when the cases' children answered (a copy of this study may be found in Section A of this notebook).

Reporting bias

- Another type of bias that may arise is "reporting bias," which may result if cases and controls respond differently to questions about personal smoking and ETS exposure.²

Publication bias

- "Publication bias" arises from the apparent failure by scientific journals to publish papers reporting negative or weakly positive results. If this occurs, the set of published investigations may not be truly representative of all the studies in the area.³

Confounding factors

- The studies did not always account for possible confounding factors. (This is addressed in more detail in the section in this notebook on confounders.)

Use of questionnaires

- All of the epidemiologic studies on the purported association between ETS exposure and disease in nonsmokers rely solely upon questionnaires about exposure, rather than upon actual exposure data.⁴ Recent studies indicate that questionnaires are an unreliable and inaccurate measure of exposure.
- Questionnaire responses about exposure vary widely when compared with actual measurements of ETS constituents in the ambient air.⁵

Histology

- Lung cancer diagnoses were not always histologically or pathologically verified.¹
- Also, the histological composition, i.e., the type of lung cancer, differed among studies (in some studies, all histological types were included; in others, some types were excluded).¹

"Data-dredging"

- Investigators often examine numerous subgroups of the study population, and may report only those conclusions which fit with their hypothesis.¹ (This is sometimes called "data-dredging.")

Misclassification

- If the personal smoking status of subjects is not accurately classified, it could result in "misclassification bias."
- One critic, Peter Lee, contends that the reported "risks" for nonsmokers are the result of bias caused by a small number of smokers who are reported in the studies as nonsmokers.⁶

Conclusion

German scientist Karl Überla discussed some criticisms of the ETS-lung cancer studies at a recent scientific symposium in Argentina:

The majority of criteria for a causal connection are not fulfilled. There is no consistency, there is a weak association, there is no specificity, the dose-effect relation can be viewed controversially, bias and confounding are not adequately excluded, there is no intervention study, significance is only present under special conditions and the biological

plausibility can be judged controversially.⁷

The eminent statistician Nathan Mantel concluded the following:

[I]t is unlikely that any epidemiological study has been, or can be, conducted which could permit establishing that the risk of lung cancer has been raised by passive smoking. Whether or not the risk is raised remains to be taken as a matter of faith.

Copies of critical papers, highlighted in yellow for useful information and in blue for adverse statements, are found at Tabs 1-7.

CRITICISMS OF THE HIRAYAMA STUDY

Numerous criticisms of the Hirayama study have been made.⁸⁻²¹ They include:

- The age distribution of the sample is not representative of the total Japanese population, particularly for women over the age of 40.⁸ When a statistical correction is made for this bias, the increased relative risk reported by Hirayama virtually disappears.
- The appropriateness of Hirayama's standardization of the data by husband's age, rather than by subject's, has been questioned.⁹⁻¹² When Kilpatrick re-analyzed the data adjusted by subject's age, the model used by Hirayama was shown to be inappropriate and the reported significantly elevated risk associated with husband's smoking was no longer apparent.
- The Hirayama study was not designed to investigate ETS exposure; it is inappropriate to use it to make conclusions about the hypothesis of an ETS-lung cancer relationship.⁸
- Errors and internal inconsistencies in the data and in risk ratios and confidence intervals have been noted and publicly acknowledged by Hirayama.¹³⁻¹⁵

- The design of the study has been criticized, e.g., use of death certificates as evidence for lung cancer is unreliable⁸; autopsy or histology results were available for only 11.5% (23 of 200) of the cases^{8,16}; use of the smoking status of the subject's husband as a surrogate measure for ETS exposure is not reliable^{8,12}; many possible confounding factors were overlooked.^{8,17}

It appears that Hirayama has never adequately addressed the criticisms; for instance, his 1990 monograph on the study persists in presenting the same data analyses that have been particularly criticized.¹⁸ In addition, Hirayama has not made his original data available for review.^{8,19,20}

A bibliography of the criticisms follows. Copies of selected papers are given at Tabs 8-20. They are highlighted in yellow for useful information and in blue for adverse statements.

CRITICISMS OF THE TRICHOPOULOS STUDY

Regarding the Trichopoulos, et al., study, the following criticisms have been made:

- In 1990, Letzel and Überla evaluated the quality of ETS-lung cancer studies.²² Based on possible sources of bias and other problems with study design, they concluded that the Trichopoulos, et al. study, in particular, is "methodologically unacceptable" and is "a textbook example of how a case-control study should not be performed." Furthermore, they reported that this study may strongly influence the outcomes of meta-analyses of the ETS-lung cancer epidemiological studies (e.g., when the Trichopoulos study was included in meta-analyses of all possible case-control study combinations, it appeared in 330 of the 353 significant study combinations).
- Methodologically, the study has been criticized for selecting cases and controls from different hospitals; for excluding patients with adenocarcinoma and with alveolar carcinoma; for the lack of histological or cytological confirmation in 35% of the cases; and for its small sample size.^{8,24} According to Überla, the small sample size means that "the statistically 'significant' results of this study may well be artefacts from chance, bias or confounding."²³

Copies of the articles referenced above, highlighted in yellow for useful information and in blue for adverse statements are found at Tabs 21-23.

REFERENCES
General Criticisms

1. Wynder, E.L. and Kabat, G.C., "Environmental Tobacco Smoke and Lung Cancer: A Critical Assessment," Indoor Air Quality, ed. H. Kasuga (Berlin, Heidelberg: Springer-Verlag, 1990): 5-15.
2. Kilpatrick, S.J., "Misclassification of Environmental Tobacco Smoke Exposure: Its Potential Influence of Studies of Environmental Tobacco Smoke and Lung Cancer," Toxicology Letters 35: 163-168, 1987.
3. Mantel, N., "Lung Cancer and Passive Smoking," British Medical Journal 294: 440, 1987.

Newcombe, R., "Towards a Reduction in Publication Bias," British Medical Journal 295: 656-659, 1987.
4. Coultas, D.B., Peake, G.T. and Samet, J.M., "Questionnaire Assessment of Lifetime and Recent Exposure to Environmental Tobacco Smoke," American Journal of Epidemiology 130(2): 338-347, 1989.

Coultas, D.B., Samet, J.M., McCarthy, J.F. and Spengler, J.D., "A Personal Monitoring Study to Assess Workplace Exposure to Environmental Tobacco Smoke," American Journal of Public Health 80(8): 988-990, 1990.
5. Coultas, D.B., Samet, J.M., McCarthy, J.F. and Spengler, J.D., "Variability of Measures of Exposure to Environmental Tobacco Smoke in the Home," American Review of Respiratory Disease 142: 602-606, 1990.
6. Lee, P.N., "Increased Risk of Lung Cancer in Non-smokers Married to Smokers: A Result of ETS Exposure or of Bias?" Indoor Air Quality, ed. H. Kasuga (Berlin, Heidelberg: Springer-Verlag, 1990): 25-36.
7. Überla, K., "Epidemiology: Its Scope and Limitations for Indoor Air Quality," Indoor Air Quality (Buenos Aires: National Academy of Sciences of Buenos Aires, Argentina, 1988): 45-60.

REFERENCES
Criticism of Hirayama, 1981

8. Überla, K. and Ahlborn, W., "Passive Smoking and Lung Cancer: A Reanalysis of Hirayama's Data," Indoor Air Quality, ed. H. Kasuga (Berlin, Heidelberg: Springer-Verlag, 1990): 333-340.
9. MacDonald, E., "Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung Cancer," British Medical Journal II, 283: 915-916, 1981.

MacDonald, E., "Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung Cancer," British Medical Journal II, 283: 1465, 1981.
10. Lee, P., "Passive Smoking," Food Chemistry and Toxicology 20: 223-229, 1982.
11. Kilpatrick, S. and Viren, J., "Age as a Modifying Factor in the Association Between Lung Cancer in Non-Smoking Women and Their Husbands' Smoking Status," Indoor and Ambient Air Quality, eds. R. Perry and P. Kirk (London: Selper, Ltd., 1988): 195-202.
12. Kilpatrick, S., "An Example of Extra-Poisson Variation Suggesting an Under-Specified Model," Present and Future of Indoor Air Quality, eds. C. Bieva, Y. Courtois and M. Govaerts (Amsterdam: Excerpta Medica, 1989): 83-90.

Kilpatrick, S., "Model Specification Effects in ETS/Nutrition Research," Indoor Air Quality, ed. H. Kasuga (Berlin, Heidelberg: Springer-Verlag, 1990): 257-271.
13. Lee, P., "Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung Cancer," British Medical Journal II, 283: 1465-1466, 1981.
14. Hirayama, T., "Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung Cancer," British Medical Journal II, 283: 1466, 1981.
15. Layard, M. and Viren, J., "Assessing the Validity of a Japanese Cohort Study," Present and Future of Indoor Air Quality, eds. C. Bieva, Y. Courtois and M. Govaerts (Amsterdam: Excerpta Medica, 1989): 177-180.
16. Grundmann, E., Miller, K.-M. and Winter, K.D., "Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung Cancer," British Medical Journal I, 282: 1156, 1981.

17. Sterling, T., "Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung Cancer," British Medical Journal I, 282: 1156, 1981.
 18. Hirayama, T., Life-Style and Mortality: A Large-Scale Census-Based Cohort Study in Japan, (Basel: Karger, 1990).
 19. Adlkofer, F., "Probleme mit dem Passivrauchen (The Problems of Passive Smoking)," Der Kassenarzt 27(51/52): 29-39, 1987. Translation.
 20. Ahlborn, W. and Überla, K., "Passive Smoking and Lung Cancer: Reanalyses of Hirayama's Data," Indoor and Ambient Air Quality, eds. R. Perry and P. Kirk (London: Selper, Ltd., 1988): 169-178.
 21. Aviado, D., "Toxicological Basis for Regulation of Indoor Air Quality," Journal of Applied Toxicology 8(3): 155-157, 1988.
- Diamond, G. and Forrester, J., "Clinical Trials and Statistical Verdicts: Probable Grounds for Appeal," Annals of Internal Medicine 98(3): 385-394, 1983.
- Gostomzyk, G., "Krank durch Passivrauchen (Disease Due to Passive Smoking?)," Munch med Wschr 124(4):16, 1982. Translation.
- Kornegay, H. and Kastenbaum, M., "Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung Cancer," British Medical Journal II, 283: 914, 1981.
- Mantel, N., "Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung Cancer," British Medical Journal II, 283: 914-915, 1981.
- Mantel, N., "Epidemiologic Investigations: Care in Conduct, Care in Analysis, and Care in Reporting," Journal of Cancer Research and Clinical Oncology 105: 113-116, 1983.
- Rutsch, M., "Non-Smoking Wives of Heavy Smokers Have a Higher Risk of Lung Cancer," British Medical Journal I, 282: 985, 1981.

REFERENCES

Criticisms of Trichopoulos, et al., 1981

22. Letzel, H. and K. Überla, "Meta-Analyses on Passive Smoking and Lung Cancer," Indoor Air Quality, ed. H. Kasuga (Berlin, Heidelberg: Springer-Verlag, 1990): 316-322.
23. Überla, K., "Lung Cancer from Passive Smoking: Hypothesis or Convincing Evidence?," International Archives of Occupational and Environmental Health 59: 421-437, 1987.
24. Heller, W.-D., "Lung Cancer and Passive Smoking," The Lancet II: 1309, 1983.

CONFOUNDING FACTORS

Introduction

According to a 1990 publication by a Swedish scientist,

Dr. Ragnar Rylander:

Studies evaluating the hypothesis of a relationship between exposure to environmental tobacco smoke and lung cancer must take into account other environmental risk or protection factors and the possibility that exposure to environmental tobacco smoke may be confounded. This has not been done in the majority of such studies. Until this has been done, the claim of causality between environmental tobacco smoke and lung cancer remains uncertain. [Emphasis added.]¹

In epidemiologic studies, confounders are variables which can affect the outcome of interest, independently of the factor under investigation. Potential confounding factors in studies of ETS and lung cancer are numerous and varied.² It is difficult to control for all of them in the design of an epidemiologic study. Following are lists of some of the possible confounders encountered in epidemiologic studies of lung cancer incidence in nonsmokers, both those specifically considering ETS and those dealing with other factors.

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Heating and Cooking Fuels

- In developing countries, the use of certain fuels (kerosene, gas, coal, liquefied petroleum gas, straw, or wood) for heating and cooking contributes to elevated levels of indoor air pollution, which may contribute to disease incidence.³
- Following earlier, limited reports⁴ on exposures to fumes from the use of various fuels, eight studies examining coal use in stoves and other indigenous heating devices in China have recently been published.⁵⁻¹² RRs as high as 14 have been reported,⁸ although most RRs are in the 1.0 to 2.0 range.^{11,12}
- Some fuels, namely, kerosene or coal and wood or straw, have been associated with a increased risk of lung cancer in Japanese women as well.^{13,14}

Cooking Techniques

- The use of certain cooking oils and some cooking techniques (i.e, stir-frying and deep frying) which produce oil vapors have been associated with increased lung cancer risks in Chinese women.^{11,15}

Air Pollution

- In addition to indoor air pollution from heating and cooking fuels, as described above, outdoor air pollution has been associated with increased lung cancer incidence in at least one epidemiologic study in northeast China.¹²

Dietary Factors

- Increased lung cancer risk has been associated with the consumption of smoked, salted, cured, pickled, processed, or spicy foods among Oriental women.¹⁸ Additionally, research suggests that wives whose husbands smoke may consume more processed and spicy foods and eat fewer fresh fruits and vegetables than do those whose husbands do not smoke.
- One study reported an elevated lung cancer risk among Oriental women associated with the consumption of green or black tea.¹⁷
- It has also been reported that nonsmokers married to smokers have lower intakes of dietary carotene, a substance associated with decreased cancer risks when consumed in sufficient amounts.¹⁸ Recently, an abstract reported an correlation between serum carotene levels and socioeconomic status; this

could be important if smoking and SES are also correlated, as has been suggested.

Occupation

- Some of the studies considering lung cancer in nonsmokers have also reported elevated relative risks associated with employment in certain fields or with occupational exposures to certain substances.^{5,11-13}

Medical and Lifestyle Factors

- Personal health factors such as menstrual cycle length and previous history of respiratory disease (including tuberculosis, pneumonia or emphysema) have been associated with increased risk for lung cancer.^{5,9,11,15}
- Family history of lung cancer has also been associated with increased lung cancer risk.^{9,11}
- An association between husband's smoking status and family lifestyle has been reported.¹⁶ Wives with husbands who were nonsmokers had better SES, were more conscientious housewives, ate better diets, had higher indices of family cohesiveness,

and had better indices of overall health than did women married to smokers.

- At least one hobby, keeping pet birds, has been associated with increased lung cancer risk.¹⁹

Conclusion

While of general importance, the question of confounders appears to be particularly relevant in studies of Asian women. Certain cultural variables (e.g., use of smoky fuels, certain cooking methods, diet) differ greatly between Asian and Western populations. The potential effects of such factors must be considered when evaluating the results of epidemiologic studies on lung cancer incidence, particularly those considering ETS exposure. Table 1 presents a comparison and summary of Asian studies to date, revealing the increasing attention paid to confounders in these studies.

Dr. Linda Koo, in her 1988 paper on lifestyle correlates, summed up the importance of confounders as follows:

[C]aution should be exercised when interpreting data on ETS. It may not be the hazards of tobacco smoke that are being evaluated, but a whole range of behaviors that result from having a smoking husband, which may in turn increase the risk for certain diseases among their wives and children.¹⁶

Table 1a. Asian Studies Included in EPA Draft Risk
Assessment: Epidemiologic Studies of Lung
Cancer in Nonsmoking Women, with Spousal Smoking Included

Study [site]			Sample Size	Spousal Smoking*	Factors Considered			
					Heating Methods/ Fuel Use	Cooking Tech- Niques	Diet	Other
Hirayama, 1981, 1984 [Japan]			91,540	(+)	--	--	--	--
Chan and Fung, 1982 [Hong Kong]			223	(-)	--	Yes	--	--
Lam, 1985 [Hong Kong]			248	(-)	--	Yes	--	Home incense burning
Akiba, et al., 1986 [Japan]			1,385	(+)	--	--	--	Radiation exposure
Gao, et al., 1987 [Shanghai]			1,407	(-)	--	Yes	Yes	Medical history; hormonal factors
Koo, et al., 1987 [Hong Kong]			225	(-)	--	--	--	--
Lam, et al., 1987 [Hong Kong]			890	(+)	--	--	--	--
Geng, et al., 1988 [Tianjin, China]			314	(+)	Yes	--	--	Medical history; occupation
Inoue and Hirayama, 1988 [Japan]			83	(+)	--	--	--	--

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Study [site]	Sample Size	Spousal Smoking*	Factors Considered			
			Heating Methods/ Fuel Use	Cooking Tech- Niques	Diet	Other
Shimizu, et al., 1988 [Japan]	180	(-)	Yes	--	Yes	Occupation

* (+) indicates a statistically significant relative risk was reported; (-) indicates the reported relative risk was not statistically significant.

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Table 1b. Asian Studies Published After EPA Draft Risk Assessment: Epidemiologic Studies of Lung Cancer in Nonsmoking Women, with Spousal Smoking Included

Study [site]	Sample Size	Spousal Smoking*	Factors Considered			
			Heating Methods/ Fuel Use	Cooking Tech- Niques	Diet	Other
He, et al., 1990 [China]	536 ⁺	(-)	Yes	Yes	--	Medical history
Sobue, et al., 1990 [Japan]	639	(-)	Yes	--	--	--
Wang, et al., 1990 [NE China]	110	(-)	Yes	--	--	Indoor and outdoor air pollution
Wu-Williams, et al., 1990 [NE China]	1,924	(+)**	Yes	Yes	Yes	Medical history; occupation
Liu, et al., 1991*** [China]	221	(-)	Yes	Yes	--	Medical history

* (+) indicates a statistically significant relative risk was reported; (-) indicates the reported risk was not statistically significant.

+ Males and females combined.

** The reported relative risk was statistically significantly negative.

***Full report on population discussed in He, et al., abstract.

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Table 1c. Ancillary Asian Studies, Not Considered in EPA Draft Risk Assessment

Study [site]	Sample Size	Spousal Smoking	Factors Considered			
			Heating Methods/ Fuel Use	Cooking Tech- Niques	Diet	Other
Koo, et al., 1984 [Hong Kong]	400	No**	--	--	--	--
Mumford, et al., 1987 [China]	--	No	Yes	--	--	--
Chapman, et al., 1988 [China]	144 ⁺	No	Yes	--	--	--
Koo, et al., 1988 [Hong Kong]	136	No	--	--	Yes	Lifestyle variables
Du and Ou, 1990 [China]	1,324	No	Yes	--	--	--
Xu, et al., 1990 [NE China]	1,077	No	Yes	Yes	Yes	Indoor and outdoor air pollution; occupation

** Other questions were asked regarding ETS.

+ Males and females combined.

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A selection of the relevant literature follows. Useful information is highlighted in yellow; problematic statements are highlighted in blue.

REFERENCES

1. Rylander, R., "Environmental Tobacco Smoke and Lung Cancer," The New England Journal of Medicine 323(12): 834, 1990.
2. Katzenstein, A.W., "An Estimate of Adult Mortality in the United States from Passive Smoking: A Response," Environment International 16: 175-193, 1990.
3. Chen, B.H., Hong, C.J., Pandey, M.R. and Smith, K.R., "Indoor Air Pollution in Developing Countries," World Health Statistics Quarterly 43: 127-138, 1990.
4. Anonymous, "Lung Cancer in South China," Oncology Times 7(6): 33, 1986.

deSerres, F.J. and Matsushima, T., "Meeting Report: Mutagenesis and Carcinogenesis by Nitropyrenes and Cancer Chemotherapeutics," Mutation Research 164: 3-8, 1986.
5. Geng, G.-Y., Liang, T.H., Zhang, A.Y. and Wu, G.L., "On the Relationship Between Smoking and Female Lung Cancer," Smoking and Health 1987, eds. M. Aoki, S. Hisamichi and S. Tominaga (Amsterdam: Excerpta Medica, 1988): 283-285.
6. Mumford, J.L., He, X.Z., Chapman, R.S., Cao, S.R., Harris, D.B., Li, X.M., Xian, Y.L., Jiang, W.Z., Xu, C.W., Chuang, J.C., Wilson, W.E. and Cooke, M., "Lung Cancer and Indoor Air Pollution in Xuan Wei, China," Science 235: 217-220, 1987.
7. Chapman, R.S., Mumford, J.L., Harris, D.B., He, X., Jiang, W. and Yang, R., "The Epidemiology of Lung Cancer in Xuan Wei, China: Current Progress, Issues and Research Strategies," Archives of Environmental Health 43(2): 180-185, 1988.
8. Du, Y.-X. and Ou, X.-L., "Indoor Air Pollution and Woman Lung Cancer," Indoor Air '90: Proceedings of the 5th International Conference on Indoor Air Quality and Climate, Toronto, Canada, July 29-August 3, 1990.
9. Liu, Z., He, X., and Chapman, R.S., "Smoking and Other Risk Factors for Lung Cancer in Xuanwei, China," International Journal of Epidemiology 20(1): 26-31, 1991.

He, X., Chen, W., Liu, Z. and Chapman, R.S., "An Epidemiological Study of Lung Cancer in Xuan Wei County, China: Current Progress," (abstract), presented at the Second Annual Meeting of the International Society for Environmental Epidemiology, Berkeley, California, August 13-15, 1990.

10. Wang, F.-L., et al., "Analysis of Risk Factors for Female Lung Adenocarcinoma in Haerbin: Indoor Air Pollution," Chinese Journal of Preventive Medicine 23(5): 270-273, 1989 (translation).
11. Wu-Williams, A.H., Dai, X.D., Blot, W., Xu, Z.Y., Sun, X.W., Xiao, H.P., Stone, B.J., Yu, S.F., Feng, Y.P., Ershow, A.G., Sun, J., Fraumeni, J.F. and Henderson, B.E., "Lung Cancer Among Women in North-East China," British Journal of Cancer 62: 982-987, 1990.
12. Xu, Z.-Y., Blot, W.J., Xiao, H.-P., Wu, A., Feng, Y.-P., Stone, B.J., Sun, J., Ershow, A.G., Henderson, B.E. and Fraumeni, J.F., "Smoking, Air Pollution, and the High Rates of Lung Cancer in Shenyang, China," Journal of the National Cancer Institute 81: 1800-1806, 1989.
13. Shimizu, H., Morishita, M., Mizuno, K., Masuda, T., Ogura, Y., Santo, M., Nishimura, M., Kunishima, K., Karasawa, K., Nishiwaki, K., Yamamoto, M., Hisamichi, S. and Tominaga, S., "A Case-Control Study of Lung Cancer in Nonsmoking Women," Tohoku Journal of Experimental Medicine 154: 389-397, 1988.
14. Sobue, T., Suzuki, R., Nakayama, N., Inubuse, C., Matsuda, M., Doi, O., Mori, T., Furuse, K., Fukuoka, M., Yasumitsu, T., Kuwabara, O., Ichigaya, M., Kurata, M., Kuwabara, M., Nakahara, K., Endo, S. and Hattori, S., "Passive Smoking Among Nonsmoking Women and the Relationship Between Indoor Air Pollution and Lung Cancer Incidence -- Results of a Multicenter Case Controlled Study," Gan to Rinsho 36(3): 329-333, 1990 (translation).
15. Gao, Y.-T., Blot, W.J., Zheng, W., Ershow, A.G., Hsu, C.W., Levin, L.I., Zhang, R. and Fraumeni, J.F., "Lung Cancer Among Chinese Women," International Journal of Cancer 40: 604-609, 1987.
16. Koo, L.C., "Dietary Habits and Lung Cancer Risk Among Chinese Females in Hong Kong Who Never Smoked," Nutrition and Cancer 11: 155-172, 1988.

Koo, L.C., Ho, J.H.-C. and Rylander, R., "Life-History Correlates of Environmental Tobacco Smoke: A Study on Nonsmoking Hong Kong Chinese Wives with Smoking Versus Nonsmoking Husbands," Soc Sci Med 26(7): 751-760, 1988.

Koo, L.C., "Environmental Tobacco Smoke and Lung Cancer: Is It the Smoke or the Diet?" Present and Future of Indoor Air

Quality, C.J. Bieva, et al., (eds.), (Amsterdam: Excerpta Medica, 1989): 65-75.

17. Tewes, F.J., Koo, L.C., Meisgen, T.J. and Rylander, R., "Lung Cancer Risk and Mutagenicity of Tea," Environmental Research 52: 23-33, 1990.
18. Sidney, S., Caan, B.J. and Friedman, G.D., "Dietary Intake of Carotene in Nonsmokers with and Without Passive Smoking at Home," American Journal of Epidemiology 129(6): 1305-1309, 1989.

Waller, K.D. and Smith, A.H., "Effects of Socioeconomic Status and Smoking on Serum Beta-Carotene," Archives of Environmental Health 46(2): 120, 1991.
19. Holst, P.A., et al., "For Debate: Pet Birds as an Independent Risk Factor for Lung Cancer," British Medical Journal 297: 1319-1321, 1988.

USE OF META-ANALYSIS: EPIDEMIOLOGIC STUDIES ON ETS AND LUNG CANCER

Introduction

The statistical procedure of meta-analysis treats the results of individual studies as individual data points in an overall analysis. It has been used effectively in combining the results of randomized, controlled clinical trials of pharmaceuticals. Such studies are eminently comparable because their methodologies and study populations are very similar.

More recently, meta-analysis has been used to analyze the results of epidemiologic studies, that is, to calculate an overall relative risk as a weighted average of the relative risks of many studies. Because of the inherent differences in study design, methodology, and sample population, especially in the case of epidemiologic studies on ETS and lung cancer, questions have been raised regarding the appropriateness of using this procedure to analyze epidemiologic data. However, meta-analysis is still being used; most recently, the U.S. Environmental Protection Agency (EPA) used a meta-analysis to calculate an estimated overall relative risk for lung cancer related to exposure to environmental tobacco smoke (ETS).¹

The EPA meta-analysis is not the first in this area. The risk estimates calculated by several other meta-analyses are given in Table 1 for comparison.²⁻⁸

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In addition to its meta-analysis on United States ETS-lung cancer studies, the recent paper by Fleiss and Gross (1991) presents a detailed criticism of the meta-analytical method, particularly as applied to the ETS literature.⁸ This is a thorough review paper and a useful reference. Some relevant quotations follow:

[T]he authors of the NRC report appear not to have followed the major guidelines proposed by Sacks, et al. For example, they did not provide a formal protocol for the meta-analysis, nor, apparently, did they give any consideration to the possibility of heterogeneous ORs across the several studies. (p. 134)

Furthermore, the question comes to mind whether the existing epidemiological studies of a possible association between exposure to ETS and the incidence of lung cancer in non-smokers are of adequate quality. Indeed, there is the question whether any of these studies meets even minimal standards of quality. (pp. 134-135)

There are many reasons for restricting attention to American studies of whether there is an elevated risk of lung cancer to non-smokers exposed to ETS relative to non-smokers not so exposed. One is that this is the population to whom policy decisions will apply and on whom those decisions should be based. (p. 135)

Odds ratios from studies in other countries, on the other hand, are derived from distributions that may differ markedly from those in the U.S., and thus the ORs themselves may not be relevant to the American experience. Genetic and lifestyle differences between the U.S. population and the populations studied elsewhere (mainly in east Asia) also argue for a meta-analysis only of U.S. studies. (p. 135)

[U]ncritical use of meta-analysis can and does lead to unsubstantiated conclusions. Only when all the issues that we have discussed are considered and possibly accounted for is it possible to apply meta-analysis so that the overall result is scientifically valid. (p. 137)

It is very unlikely that the biases present in the epidemiological studies of the possible association between exposure to ETS and the risk of lung cancer can ever be removed. The meta-analysis performed by the NRC must either be completely discounted or, as Stein concluded so succinctly in another context, considered a mere 'computational exercise.' (p. 137)

(An editorial comment on this paper by Spitzer is also included.⁹)

Copies of some of the referenced articles are included at Tabs 1-4. They are highlighted in yellow for useful information, and in blue for adverse information.

Table 1. Results of Meta-Analyses of Epidemiologic Studies of Spousal Smoking and Female Lung Cancer

<u>Meta-Analysis</u>	<u>Summary Risk Estimate</u>	<u>Studies Included</u>
Wald, et al., 1986	1.35 (95% CI 1.19-1.54)	13; 10 case-control, 3 cohort
NRC, 1986	1.32 (95% CI 1.16-1.51)	13; 10 case-control, 3 cohort
Blot and Fraumeni, 1986	1.3 (95% CI 1.1-1.5)	12; 10 case-control, 2 cohort
Wells, 1988	1.44 (95% CI 1.26-1.66)	17; 14 case-control, 3 cohort
EPA, 1990	1.41 (95% CI 1.26-1.57)	22; 19 case-control, 3 cohort
	1.25 (95% CI 1.03-1.52)	8 U.S. studies; 7 case-control, 1 cohort
Letzel and Überla, 1990	1.118 1.076	12; 10 case-control, 2 cohort 11; 9 case-control (Trichopoulos excluded), 2 cohort
Fleiss and Gross, 1991	1.12 (95% CI 0.95-1.30)	9 U.S. studies; 8 case-control, 1 cohort
Layard and LeVois, 1991 (unpublished)	1.08 (95% CI 0.96-1.22)	26; 23 case-control, 3 cohort

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REFERENCES

1. United States Environmental Protection Agency, "Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children," (Review Draft) EPA/600/6-90/006A, May, 1990.
2. Wald, N.J., Nanchahal, K., Thompson, S.G. and Cuckle, H.S., "Does Breathing Other People's Tobacco Smoke Cause Lung Cancer?," British Medical Journal 293: 1217-1222, 1986.
3. National Research Council, Environmental Tobacco Smoke: Measuring Exposure and Assessing Health Effects (Washington: National Academy Press, 1986).
4. Blot, W.J. and Fraumeni, J.F., "Passive Smoking and Lung Cancer," Journal of the National Cancer Institute 77(5): 993-1000, 1986.
5. Wells, A.J., "An Estimate of Adult Mortality in the United States from Passive Smoking," Environment International 14: 249-265, 1988.
6. Letzel, H. and Überla, K., "Meta-Analyses on Passive Smoking and Lung Cancer," Indoor Air Quality, ed. H. Kasuga (Berlin, Heidelberg: Springer-Verlag, 1990): 316-322.
7. Layard, M.W. and LeVois, M.E., Letter to Dr. Donald G. Barnes, Director of the Science Advisory Board, United States Environmental Protection Agency, April 9, 1991.
8. Fleiss, J.L. and Gross, A.J., "Meta-Analysis in Epidemiology, with Special Reference to Studies of the Association Between Exposure to Environmental Tobacco Smoke and Lung Cancer: A Critique," Journal of Clinical Epidemiology 44(2): 127-139, 1991.
9. Spitzer, W.O., "Meta-Meta-Analysis: Unanswered Questions About Aggregating Data," Journal of Clinical Epidemiology 44(2): 103-107, 1991.

RISK ESTIMATES FOR NONSMOKER LUNG CANCER
BASED UPON MODELING PROCEDURES

- In 1985, Repace and Lowrey published an article claiming that exposure to ETS is responsible for 500 to 5,000 lung cancer deaths per year in the United States.¹ This report received extensive press coverage upon its release.
- The report contains two highly theoretical models for estimating risks of lung cancer from ETS exposure. One model relies upon a "reinterpretation" of the epidemiologic studies of lung cancer in nonsmokers; the second model estimates lung cancer mortality among nonsmokers based on a single study dealing with the Seventh Day Adventists, a religious group known for its vigorous opposition to smoking.
- Critics of the Repace and Lowrey approach have pointed out that the estimates are based on errors and "unrealistic assumptions" which result in overestimations of exposure.² One analysis of the model showed that, depending on the assumptions and input data used, the estimates are inherently inaccurate and may vary by as much as 300-fold.³ Another scientist noted that the exposure and dose levels used in the modeling exercise were not based on actual measurements; such measurements reported elsewhere range from "ten- to one-hundred-fold less than that in the Repace and Lowrey model."⁴

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- Other criticisms have focused on the report's methods of analysis,⁵⁻⁷ and suggest that Repace and Lowrey failed to control for other confounding factors, and that their model did not provide "the very statistical bases of estimation procedures."⁴
- Repace and Lowrey's estimate of nonsmoker lung cancer risks in the workplace was also criticized by scientists who noted that none of the epidemiologic studies of ETS exposure and disease in nonsmoking working women report a statistically significant increase in risk.²
- Two British researchers, Darby and Pike, published a paper in 1988 describing another type of mathematical model which predicted potential effects from ETS exposure based on data from a study on active smoking.⁸ Even when adjustments were made for childhood exposure to ETS, the authors reported that the model predicted a risk for nonsmokers that was smaller than "the underlying background risk for lung cancer." They concluded that their model could not explain the difference between risks reported for nonsmokers in epidemiologic studies and the low levels of ETS exposure reported in other studies.

- The Darby and Pike model was criticized in 1990 by Wald, et al., authors of one of the earlier meta-analyses on the epidemiologic studies of ETS exposure and lung cancer incidence.⁹ Wald's group questioned Darby and Pike's conclusion that there was a discrepancy between risks estimated by epidemiologic studies and by exposure data. Darby and Pike replied that the existing cotinine data employed by Wald, et al., were possibly both insufficient and inappropriate to allow an adequate comparison to be made with the epidemiologic data.¹⁰

REFERENCES

1. Repace, J.L. and Lowrey, A.H., "A Quantitative Estimate of Nonsmokers' Lung Cancer Risk from Passive Smoking," Environment International 11(1): 3-22, 1985.
2. Arundel, A., Irwin, T. and Sterling, T., "Nonsmoker Lung Cancer Risks from Tobacco Smoke Exposure: An Evaluation of Repace and Lowrey's Phenomenological Model," Journal of Environmental Science and Health C4(1): 93-118, 1986.
3. Arundel, A., Sterling, T. and Weinkam, J., "Never Smoker Lung Cancer Risks from Exposure to Particulate Tobacco Smoke," Environment International 13: 409-426, 1987.
4. Lebowitz, M.D., "The Potential Association of Lung Cancer with Passive Smoking," Environment International 12: 3-9, 1986.
5. Johnson, C. and Letzel, H., "Letter to the Editors," Environment International 12: 21-22, 1986.
6. Burch, P.R.J., "Health Risks of Passive Smoking: Problems of Interpretation," Environment International 12: 23-28, 1986.
7. Kilpatrick, S.J., "Letter to the Editors," Environment International 12: 29-31, 1986.
8. Darby, S.C. and Pike, M.C., "Lung Cancer and Passive Smoking: Predicted Effects from a Mathematical Model for Cigarette Smoking and Lung Cancer," British Journal of Cancer 58: 825-831, 1988.
9. Wald, N., Nanchahal, K., Cuckle, H. and Thompson, S., "Letter to the Editor: Lung Cancer and Passive Smoking," British Journal of Cancer 61: 337, 1990.
10. Darby, S.C. and Pike, M.C., "Response to the Letter from Dr. Wald," British Journal of Cancer 61: 337-338, 1990.



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ETS AND CANCER OF SITES OTHER THAN THE LUNG

Introduction

A presenter at the recent McGill Symposium in Montreal, Canada, described the then-available epidemiologic studies on ETS and cancer other than the lung as follows:

These nine studies provide insufficient data to evaluate the effect of ETS on cancer other than of the lung. The reported associations are weak and inconsistent, and are subject to the potential effects of biases and uncontrolled confounding factors . . .

These studies concern a variety of cancer sites; the publications on each are briefly summarized below. Highlighted copies of the papers on cancer at other sites are found at Tabs 1-11.

All Cancers Combined

- Several studies have presented risk estimates for overall cancer incidence, regardless of site, among individuals reporting ETS exposure. This procedure disregards differences in etiology, mechanism and confounding factors among the various types of cancer; nevertheless, some authors have presented data in this fashion.

Hirayama (1984) reported a significant elevation in risk for "cancer of all sites," in nonsmoking women whose husbands

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smoked; he attributed the elevation to increased risks for lung, nasal sinus, and brain cancers.²

Miller (1984) reports on a "case-control" study conducted in Pennsylvania by interviewing the surviving relatives of women whose death notices were published in a local newspaper.³ Miller reported an overall odds ratio of 1.40 for "death due to cancer" among women whose husbands smoked. Questions can be asked about the accuracy of the amount of recall required of the relatives in this study.

In an abstract, Reynolds, et al., (1987) reported that a record-linkage study in Alameda County, CA concluded that nonsmoking women married to smokers had a 70% higher risk of cancer incidence at all sites, and that they had an approximate relative risk of 7.0 for "smoking-related cancers."⁴ The abstract provides insufficient information to judge the quality of the study; the reported risk estimates should be viewed with caution.

Sandler, et al., (1989) reported statistically nonsignificant point estimates of 1.01 (males) and 1.00 (females) for all cancers in persons reporting ETS exposure.⁵ The authors' subdivision of the category into "smoking-related" and "other" cancers yielded no statistically significant risk estimates. This study was criticized by Holcomb (1989) as being "poor science" and

"inadequately designed."⁶

Brain and Nasal Sinus Cancers

- A single report claims to show an increased risk for brain and nasal sinus cancers associated with marriage to a smoker. No other researchers have been able to replicate these findings and they must be considered isolated.

Only Hirayama (1984), reporting further on his study of Japanese women, has reported statistically significant associations in women between brain and nasal sinus cancers and spousal smoking.²

Breast Cancer

- Some claims have been made for a relationship between husband's smoking and breast cancer in nonsmoking women.

Sandler, et al., (1985) reported a statistically non-significant increased risk for breast cancer in non-smoking women and statistically significant elevated risks for cancers of the endocrine system associated with early life (i.e., childhood) exposure to parental smoking.⁷

Hirayama (1984), in his discussion of his claim that his data support an elevated risk for all cancers in nonsmoking women whose husbands smoke, suggested that part of the reported increase might be due to breast cancer.² In a 1991 article, Wells reports a statistically nonsignificant increased risk of breast cancer using additional data supplied by Hirayama.⁸

Bladder Cancer

- Two case-control studies have specifically examined bladder cancer incidence; neither reported an association between bladder cancer and exposure to ETS at home or at work.

The 1986 Kabat, et al., paper reported that cases and controls in this study did not differ significantly in reporting "sidestream smoke exposure" at home, at work or in transportation.⁹ Neither did they differ significantly in whether or not their spouse smoked. The authors concluded that "exposure to sidestream smoke" is not an important factor in bladder cancer in nonsmokers.

The second study to report on bladder cancer is by Burch et al. (1989).¹⁰ It was conducted in Alberta and Ontario, Canada. None of the reported relative risks was statistically significant. The authors concluded that there was no evidence for an effect of

"passive smoking" on bladder cancer incidence in smokers or nonsmokers.

Cervical Cancer

- Two studies have reported on ETS exposure and the incidence of cervical cancer. Both fail to account sufficiently for confounding factors.

Statistically significant elevated risks for cervical cancer were reported in a 1985 study by Sandler, et al., of patients in North Carolina.¹¹ This study has been criticized because it did not control for known risk factors such as sexual activity, which is strongly correlated with incidence of cervical cancer.

Slattery, et al., (1989), in a study of women in Utah, reported a statistically significant increased risk of cervical cancer in non-smokers who reported three or more hours of ETS exposure per day (risk estimate of 3.43, 95% CI 1.23-9.54).¹² Although the researchers adjusted for age, church attendance, education and number of sexual partners, these variables do not account for all factors that may contribute to disease.

Zang, Wynder and Harris authored a letter in response to the Slattery, et al., study.¹³ They wrote:

[T]here clearly is undermatching of control patients with regard to important risk factors including sexual activity, religious background, and education. . . . Since the previously mentioned risk factors are correlated highly with one another as well as with active and passive smoking, the risk estimates relating smoking and cervical cancer may be subject to substantial bias and confounding. . . . In fact, the adjusted odds ratios are probably no more than the leftover effect of variables controlled imperfectly by logistic regression.

In a response, Slattery acknowledged that her group's conclusions "should be verified in other studies."¹⁴

Childhood Cancers

- Two papers have claimed that their data show that childhood exposure to ETS is related to increased incidence of certain childhood cancers.

Grufferman, et al., (1982) reported a statistically significant relative risk of 3.9 (95% CI 1.5-9.6) for father's cigarette smoking for childhood rhabdomyosarcoma in a case-control study in North Carolina.¹⁵ Only 33 cases were included in the study; only 23 cases were included in the analysis of father's smoking. Conversely, for the 8 cases with maternal smoking, the reported relative risk was 0.8 (95% CI 0.3-2.0). An extremely

large number of analyses was conducted in this study, suggesting the possibility of data-dredging.

A recent study (John, et al., 1991) reported associations for father's smoking during pregnancy (i.e., a surrogate for ETS exposure of the pregnant woman) in the absence of maternal smoking, with several indices of childhood cancer: all cancers combined (OR = 1.2, 95% CI 0.8-2.1), acute lymphocytic leukemia (OR = 1.4, 95% CI 0.6-3.1), lymphomas (OR = 1.6, 95% CI 0.5-5.4) and brain cancer (OR = 1.6, 95% CI 0.7-3.5).¹⁶ Not one of the associations was statistically significant.

Conclusion

- The studies concerning ETS exposure and cancer other than of the lung are few in number and subject to the same criticisms applicable to the lung cancer studies, e.g., "data-dredging," no assessment of exposure, inadequate control for confounding factors. Additionally, there are only one or two reports on a given cancer endpoint. Without replication of the results, it is not possible to reach any conclusion about ETS exposure and non-pulmonary cancer incidence.

REFERENCES

1. Layard, M.W., "Environmental Tobacco Smoke and Cancer: The Epidemiologic Evidence," Environmental Tobacco Smoke: Proceedings of the International Symposium at McGill University 1989, eds. D. Ecobichon and J. Wu, (Lexington, Massachusetts: Lexington Books, 1990): 99-115.
2. Hirayama, T., "Cancer Mortality in Nonsmoking Women with Smoking Husbands Based on a Large-Scale Cohort Study in Japan," Preventive Medicine 13: 680-690, 1984.
3. Miller, G.H., "Cancer, Passive Smoking and Nonemployed and Employed Wives," The Western Journal of Medicine 140: 632-635, 1984.
4. Reynolds, P., Kaplan, G.A. and Cohen, R.D., "Passive Smoking and Cancer Incidence: Prospective Evidence from the Alameda County Study," (abstract) American Journal of Epidemiology 126(4): 767, 1987.
5. Sandler, D.P., Comstock, G.W., Helsing, K.J. and Shore, D.L., "Deaths from All Causes in Non-Smokers Who Lived with Smokers," American Journal of Public Health 79: 163-167, 1989.
6. Holcomb, L.C., "Risk to Passive Smokers," (letter to the editor) American Journal of Public Health 79(10): 1432, 1989..
7. Sandler, D.P., Everson, R.B., Wilcox, A.J. and Browder, J.P., "Cancer Risk in Adulthood from Early Life Exposure to Parents' Smoking," American Journal of Public Health 75(5): 487-492, 1985.
8. Wells, A.J., "Breast Cancer, Cigarette Smoking, and Passive Smoking," (letter to the editor) American Journal of Epidemiology 133(2): 208-210, 1991.
9. Kabat, G.C., Dieck, G.S. and Wynder, E.L., "Bladder Cancer in Nonsmokers," Cancer 57: 362-367, 1986.
10. Burch, J.D., Rohan, T.E., Howe, G.R., Risch, H.A., Hill, G.B., Steele, R. and Miller, A.B., "Risk of Bladder Cancer by Source and Type of Tobacco Exposure: A Case-Control Study," International Journal of Cancer 44: 622-628, 1989.
11. Sandler, D.P., Everson, R.B. and Wilcox, A.J., "Passive Smoking in Adulthood and Cancer Risk," American Journal of Epidemiology 121: 37-48, 1985.

12. Slattery, M.L., Robison, L.M., Schuman, K.L., French, T.K., Abbott, T.M., Overall, J.C. and Gardner, J.W., "Cigarette Smoking and Exposure to Passive Smoke Are Risk Factors for Cervical Cancer," Journal of the American Medical Association 261: 1593-1598, 1989.
13. Zang, E.A., Wynder, E.L. and Harris, R.E., "Exposure to Cigarette Smoke and Cervical Cancer," (letter to the editor) Journal of the American Medical Association 262(4): 499, 1989.
14. Slattery, M.L., "Exposure to Cigarette Smoke and Cervical Cancer: In Reply," (letter to the editor) Journal of the American Medical Association 262(4): 499, 1989.
15. Grufferman, S., Wang, H.H., DeLong, E.R., Kimm, S.Y.S., Delzell, E.S. and Falletta, J.M., "Environmental Factors in the Etiology of Rhabdomyosarcoma in Childhood," Journal of the National Cancer Institute 68(1): 107-113, 1982.
16. John, E.M., Savitz, D.A. and Sandler, D.P., "Prenatal Exposure to Parents' Smoking and Childhood Cancer," American Journal of Epidemiology 133(2): 123-132, 1991.

ETS and Heart Disease

Introduction

This notebook discusses and provides copies of the public literature bearing directly on the claim that environmental tobacco smoke (ETS) is related to heart disease. Most of this literature is epidemiological, with a current total of 11 studies presenting data on a possible statistical association between ETS and heart disease incidence or mortality.

These epidemiological reports are important because they are the primary basis for claims of an elevated heart disease risk in nonsmokers exposed to ETS. However, the literature also contains claims of special harm in compromised individuals, such as heart disease patients, or regarding biochemical effects that might mediate an adverse effect of ETS on heart disease incidence or mortality. Accordingly, this notebook also includes several laboratory and statistical reports dealing with ETS and exercise performance, particularly in angina patients, or with biochemical factors suggested as involved in the development of heart disease.

Each of the articles included in this notebook has been highlighted in blue and yellow. The blue highlighting identifies the most notable comments supporting a relationship of ETS with heart disease, or that are otherwise adverse regarding tobacco or smoking. The yellow highlighting identifies comments that

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challenge, or at least that are concessionary concerning, the potential involvement of ETS or tobacco in disease causation.

The initial section of this notebook contains an overview and discussion of the literature. The literature itself is grouped into four appendices. Appendix A (Tabs 1-13) contains the primary epidemiological reports, consisting of 11 studies reported in 13 articles. A summary and discussion of major criticisms is provided for each individual study. Appendix B (Tabs 14-17) contains the major meta-analyses and reviews concluding that ETS is associated with an elevated heart disease risk. Appendix C (Tabs 18-23) contains the primary reviews which have judged that the data are inadequate to conclude that ETS is related to heart disease. Appendix D (Tabs 24-35) contains a mixed group of articles which provide data concerning ETS in relation to exercise performance, potential effects in heart patients or in relation to cardiovascular biochemical and cellular processes. Short summaries are provided with the articles in Appendix D. If notable letters to the editor or other editorial comments were published concerning any of the articles in this notebook, these materials were also included.

Epidemiologic Reports and Reviews

Reports with original data

There are currently 11 studies (in 13 reports) presenting epidemiological data on a possible statistical association between ETS and heart disease incidence and mortality. There are 13 reports, because for two studies, the data were presented in two separate articles. It should be emphasized, however, that the epidemiological reports on the heart disease issue include several scientifically weak sources, particularly meeting abstracts. Furthermore, all of these studies are open to serious methodological criticisms. Summaries of the individual studies, as well as a list of the major criticisms of each, are provided with the highlighted copies of the articles in Appendix A.

The ETS associated risks reported in the 11 epidemiological studies are summarized in the following table.

ETS/Heart Disease Epidemiological Reports

	<u>Sex</u>	<u>Reported Risk</u>	<u>Statistical Testing</u>
Butler (1990) ¹	F	RR = 1.40	0.51 - 3.84 (95% CI)
Garland et al. (1985) ²	F	RR = 2.7	p ≤ .10
<u>Ctrl vs. ETS</u>			
Gillis et al. (1984) ³	M	31 vs 45 per 10 ⁴ /yr	No stat. test rpted.
	F	4 vs 12 per 10 ⁴ /yr	No stat. test rpted.
*He, et al. (1989) ⁴	F	OR = 1.50	p < .01
*Helsing, et al. (1988) ⁵	M	RR = 1.31	1.1-1.6 (95% CI)
	F	RR = 1.24	1.1-1.4 (95% CI)
Hirayama (1984) ⁶	F	RR = 1.31 (husbands smoking ≥ 20 cigs/day)	1.06-1.63 (90% CI)
*Hole, et al. (1989) ⁷	M+F	RR = 2.01	1.21-3.35 (95% CI)
Humble, et al. (1990) ⁸	F	RR = 1.59	0.99-2.57 (95% CI)
Lee, et al. (1986) ⁹	M+F	RR = 1.03	0.65-1.62 (95% CI)
*Martin, et al. (1986) ¹⁰	F	RR = 3.4	p < .01
Palmer, et al. (1988) ¹¹	F	RR = 1.2	No stat. test rpted.
*Sandler, et al. (1989) ¹²	M	RR = 1.31	1.05-1.64 (95% CI)
	F	RR = 1.19	1.04-1.36 (95% CI)
Svendsen, et al. (1987) ¹³	M	RR = 2.23	0.72-6.92 (95% CI)

NOTE: Gillis, et al. (1984) and Hole, et al. (1989) are based on the same study. Also, Helsing, et al. (1988) and Sandler, et al. (1989) are based on the same study.

*Reported to be statistically significant at the 95% level of confidence.

In an overall evaluation of the epidemiological reports, it is important to consider the issue of statistical significance. Some fluctuation in disease or mortality rates will occur simply by chance alone. Hence, when these rates are compared, as in risk ratios, it is necessary to apply a standard to determine the statistical likelihood that an apparent elevation or reduction in risk reflects chance variation or whether it reflects an actual difference in the comparison groups. The traditional scientific standard is to require that a statistical test indicate at least a 95% probability that an observed difference reflects a true effect. Stated in reverse, this would mean that the standard only allows a 5% probability that the result was due to chance.

When discussing relative risks, if the disease or mortality rates are equivalent in the comparison groups, this will be reflected in a ratio of 1.0. When a statistical test is performed, the 95% standard is met when the 95% confidence intervals are reported not to include 1.0. Sometimes a "p" value is given, which states the probability that an observation is due to chance. Hence, a statement of " $p < .05$ " means that the observation could have occurred by chance less than 5% of the time. To state " $p < .05$ " or to provide 95% confidence intervals that do not include 1.0, are equivalent indications of statistical significance.

Only four of the 11 epidemiological studies regarding ETS and heart disease report a statistically significant result at the 95% level of confidence. (1) He, et al. (1989), a Chinese language report based on only 34 female heart disease patients; (2) Helsing, et al. (1988)/Sandler, et al. (1989), a study based on a Maryland census in which the information regarding spousal smoking (used to estimate ETS exposure) was from 1963; (3) Hole, et al. (1989), a Scottish study based on only 84 heart disease deaths; and (4) Martin, et al. (1988), a report based on 23 women who reported having a heart attack and which was given a conference but apparently not otherwise accepted for publication.

In sum, seven of the 11 studies of ETS exposure and heart disease have failed to report a statistically significant association. In the four studies that have claimed a statistically significant relationship, two were from outside the United States. Three were very small-scale. All of these studies suffer from a variety of serious methodological weaknesses.

A list of the most common weaknesses in the individual studies is provided below. It will be recognized that these are characteristic of epidemiological studies of ETS in general, not simply those relating to heart disease. For a more detailed discussion of the criticisms applicable to each study, see Appendix A.

1. Small sample sizes.
2. Lack of statistical significance, or failure to test for statistical significance.
3. Potential misclassification of the smoking status of study participants.
4. Inadequate assessment of ETS exposure.
5. Failure to control adequately for biases stemming from potential confounding variables.
6. Failure to confirm causes of death via autopsy or other histological methods.

Reviews claiming ETS-associated risk

Despite the scientific weaknesses in the epidemiologic literature on ETS and heart disease, four recent reviews have concluded that ETS is associated with an increased risk of heart disease and that, in fact, such exposure causes a large number of deaths each year. Copies of these reviews are provided in Appendix B. Each of these reviews attempted to estimate an overall risk based on the combined data from the epidemiologic studies. These estimated risk ratios and the associated 95% confidence intervals are provided in the following table.

Meta-Analyses and Reviews of ETS-Heart Disease Data

		RR	95% CI
Wells (1988) ¹⁴	Males	1.31	(1.1-1.6)
	Females	1.23	(1.11-1.36)
	<u>Home</u>		
Kawachi, et al. (1989) ¹⁵	Males	1.3	(1.1-1.6)
	Females	1.2	(1.1-1.4)
	<u>Workplace</u>		
	Males	2.3	(1.4-3.4)
	Females	1.9	(1.4-2.5)
Kristensen (1989) ¹⁶	Both sexes	≈ 1.3	
Glantz and Parmley (1991) ¹⁷	Both sexes	1.3	(1.2-1.4)

These estimates were generally derived from the statistical technique known as meta-analysis. (The Kristensen article appears to be an exception, in that the estimated 1.3 relative risk was apparently based on an informal estimation and no confidence intervals were given.) Although these reviews varied somewhat in form, detail and focus, the estimates were generally similar, about 1.3, reflecting a 30% elevation in risk associated with ETS exposure.

The Kawachi, et al. (1989) discussion was fairly narrowly focused on New Zealand. The Kristensen (1989) discussion was a

limited part of a larger discussion of factors involved in cardiovascular diseases and the work environment. Thus, the major reviews, both of which clearly involved meta-analytic techniques, were those by Wells in 1988 and by Glantz and Parmley in 1991. These two reports are discussed further below.

A. Judson Wells, a consultant to the American Lung Association, statistically combined the data from several reports on ETS and heart disease, including both prospective (cohort) and case-control studies. He then calculated overall relative risks (ETS exposed versus nonexposed) for lung cancer (1.44 for females; 2.1 for males), cancers other than lung (1.16 for females; no risk elevation for males) and heart disease (1.23 for females; 1.31 for males). He also estimated numbers of death related to these disease categories, claiming that ETS exposure results in 46,000 deaths per year in nonsmokers. Of these, 3,000 are claimed to be from lung cancer. For cancers other than the lung, he calculated that ETS exposure results in 11,000 annual deaths. The largest number of deaths from ETS exposure was claimed to be due to heart disease. He claimed that 32,000 nonsmoker heart disease deaths per year stem from ETS exposure.

The most recent, and certainly the most widely publicized, review of ETS and heart disease was undertaken by two authors from the Department of Medicine, University of California, San Francisco.

In their 1991 paper, Stanton Glantz and William Parmley conclude that ETS exposure is statistically associated with an estimated 30% increase (relative risk of 1.3) in heart disease risk in nonsmokers. They argue that this translates into 37,000 heart disease deaths in nonsmokers stemming from ETS exposure. Glantz and Parmley also discuss a number of biochemical and experimental studies which purportedly support the biological plausibility of such a relationship.

In evaluating the claims by Wells and by Glantz and Parmley, it should be emphasized that meta-analysis, the technique from which they derive their risk estimates, is appropriately used only when the underlying studies are highly similar and of high quality. If the underlying studies are based on different populations and procedures and suffer from serious methodological weaknesses, then any meta-analysis will consequently be invalidated.

The above considerations are directly applicable to an evaluation of the risk claims regarding ETS and heart disease. These claims are based on meta-analyses of a small group of epidemiological studies reporting a relationship between ETS exposure and an increased risk of heart disease. In general, these studies deal with spousal smoking and assess heart disease risk in the nonsmoking spouse. Otherwise, these studies used widely disparate methodologies, study populations and endpoints. Several

are very weak, preliminary, available only in abstract form, or are based on such scanty data that they quite arguably are not sufficiently reliable or valid even to be considered seriously in a meta-analysis. Appendix A contains discussions of the major flaws in the individual studies.

Reviews emphasizing inconclusiveness of the data

Reviews such as those by Wells and by Glantz and Parmley often receive a great deal of publicity. However, it is important to recognize that there have been a number of other examinations of the data concerning ETS and heart disease. Several important reviews have concluded that the data on this issue are equivocal and inadequate to support claims of an increased heart disease risk in nonsmokers exposed to ETS.

The first major reviews of the epidemiological data on ETS and heart disease appeared in 1986. In that year, a report of the United States Surgeon General¹⁸ examined the available data and judged that "no firm conclusion" (p. 10) could be made regarding a possible relationship between ETS and heart disease. Also in 1986, a similar evaluation appeared from a committee of the National Research Council of the National Academy of Sciences.¹⁹ This committee calculated that any potential heart disease risk related to ETS would be "difficult to detect or estimate reliably" from

epidemiological studies, and would be "the same order of magnitude as what might arise from expected residual confounding due to unmeasured covariates." (p. 263)

Thus, both the 1986 Surgeon General's Report and the National Research Council report judged that the data were insufficient to allow a conclusion that ETS exposure is a cause of heart disease. Even the 1991 review by Glantz and Parmley recognized this as a "reasonable" position, at least in 1986. On the other hand, Glantz and Parmley argued that data published since 1986 warrant that this conclusion be modified. However, other scientists have undertaken more balanced and critical reviews of the more recent data and have judged that it remains inconclusive. The four most significant of these reviews, and their conclusions, are as follows:

a. At a major conference on ETS held at McGill University in 1989, Lawrence Wexler, of the New York Medical College, concluded that recent data did not provide a basis for altering the earlier conclusions by the Surgeon General and National Research Council concerning ETS and cardiovascular disease.

Based on the available evidence, it is this author's opinion that it has not been demonstrated that exposure to ETS increases the risk of cardiovascular disease. (p. 139)²⁰

b. A similar evaluation was made by two scientists from the United Kingdom, who reviewed the literature on ETS and heart disease and presented their conclusions at an international conference on indoor air quality held in Lisbon, Portugal in April 1990.

It is concluded that no increased risk of cardiovascular disease can be associated unequivocally with exposure to ETS, and it seems probable that this will continue to be the case until specifically designed trials are instigated, and some objective measure of degree of exposure can be devised. (p. 215)²¹

c. Another scientific review of this literature was performed by two physicians from the University of Munich, Germany and given at an international conference in Hungary in June 1990. The conclusion was similar.

Taking into account the small increase in coronary risk in passive smokers as compared to non-exposed subjects and also the low validity and small number of epidemiological studies available and the fact that their results are at least inconsistent, a relationship between passive smoking and cardiovascular diseases cannot be established on these data. (p. 6)²²

d. In a 1991 book discussing a wide range of issues involving ETS, the literature on heart disease was reviewed by Alan Armitage, former director of toxicology of a major European research laboratory and now head of pharmacology at

the Tobacco Research Council Laboratories in the United Kingdom. He judged that the scientific data have not established an increased heart disease risk in nonsmokers exposed to ETS.

It is clear that the evidence for a harmful effect of ETS in enhancing CHD [coronary heart disease] risk in non-smokers is not very convincing. . . . (p. 114)²³

Studies Involving Exercise Performance, Heart Disease Patients and Biochemical Measurements

There are several experimental and biochemical studies that have been cited in the literature as supporting an increase in heart disease risk stemming from ETS exposure. A few of these reports claim that ETS exposure adversely effects exercise capacity and that in the case of heart disease patients, this can lead to attacks of angina (heart pain). Other reports have attempted to demonstrate that ETS exposure adversely affects some aspect of cardiovascular function, such as blood clotting (platelets), myocardial respiration (oxygen usage) or cholesterol levels. These articles, with brief summaries, are provided in Appendix D.

In an overall evaluation of these studies, it is important to note that they constitute a relatively minor aspect of the ETS/heart disease issue. That is, the claim that ETS increases the risk of heart disease is a statistical statement based on epidemiological reports. Once having made that statement, various

kinds of studies dealing with cardiovascular or exercise performance or with mechanisms might be marshalled to argue for its plausibility. On the other hand, without the epidemiological underpinning, such studies would probably be much less notable since there would be nothing that they would be attempting to explain.

In the area of exercise performance, there are three primary studies. In one of these, a 1985 report by McMurray, et al.,²⁴ healthy subjects were used and ETS exposure was claimed to have an adverse effect on exercise performance. Two other studies, one by Aronow (1978)²⁵ and the other by Khalfen and Klochkov (1987)²⁶ used angina patients. In somewhat similar study designs, both reports claimed that when these heart disease patients were exposed to ETS, they were not able to exercise as long before experiencing angina. The credibility of the Aronow report has been widely challenged in the literature. The Khalfen and Klochkov report is a Russian language article about which relatively little is known. Regarding any of the exercise performance studies, whether with healthy or heart disease patients, a general criticism is that when dealing with ETS, it is almost impossible to "blind" either the experimenter or the subjects with regard to ETS exposure. Thus, the possibility is always open that some subjective factor may influence the results.

There are very limited data attempting to demonstrate that ETS adversely affects some process that might be involved in blood clotting (thrombus formation) or atherosclerosis. The primary focus has been on the possibility that ETS may increase the tendency of certain blood components, known as platelets, to stick together. This claim has been made based mainly on data in four published reports. Three of these are from the same Austrian research group. (Sinzinger and Kefalides, 1982²⁷; Burghuber, et al., 1986²⁸; Sinzinger and Virgolini, 1989²⁹) Of these three, one is merely a letter to the editor (Sinzinger and Kefalides, 1982) and another is a German language article with only an English abstract (Sinzinger and Virgolini, 1989). The fourth report, Davis, et al., (1989)³⁰ is from a group of researchers in Kansas City, Missouri. It suffers from serious methodological weaknesses, particularly its failure to establish a proper control condition.

Finally, there are two reports of children which assessed cholesterol and other blood components in relation to parental smoking status (Moskowitz, et al., 1990³¹; Pomrehn, et al., 1990³²), one of which (Pomrehn, et al., 1990) is only available as an abstract from a meeting presentation. Both reports claimed that parental smoking was associated with decreases in HDL cholesterol, which some literature has argued may be associated with heart disease risk. These studies measured components of blood as the endpoint, but are essentially epidemiological studies in that they,

at best, may suggest statistical correlations. As such, they suffer from weaknesses characteristic of other epidemiological studies of ETS exposure, especially difficulties in controlling for potential confounding variables and inadequate assessment of ETS exposure. Furthermore, the potential significance of blood values in relation to later heart disease risk in a group of children is highly speculative.

This notebook also contains a group of three articles relating to research from a Czechoslovakian group, which claims that "passive smoking" has an adverse effect on the heart's use of oxygen.^{33 34 35} These were animal studies involving smoke exposure to rabbits. They clearly involved a design intended to mimic "active" smoking, and are included in this notebook merely because they were erroneously discussed in the 1991 Glantz and Parmley paper as providing data relevant to ETS exposure.

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Endnotes

1. Butler, T., "The Relationship of Passive Smoking to Various Health Outcomes Among Seventh-Day Adventists in California," Presented at the Seventh World Conference on Tobacco and Health, Abstract, 1990.
2. Garland, C., Barrett-Connor, E., Suarez, L., Criqui, M.H. and Wingard, D.L., "Effects of Passive Smoking on Ischemic Heart Disease Mortality of Nonsmokers: A Prospective Study," American Journal of Epidemiology 121(5): 645-650, 1985.

Garland, C., Barrett-Connor, E., Suarez, L., Criqui, M.H. and Wingard, D.L., "Effects of Passive Smoking on Ischemic Heart Disease Mortality of Nonsmokers: A Prospective Study," Erratum, American Journal of Epidemiology 122: 1112, 1985.
3. Gillis, C.R., Hole, D.J., Hawthorne, V.M. and Boyle, P., "The Effect of Environmental Tobacco Smoke in Two Urban Communities in the West of Scotland." In: ETS - Environmental Tobacco Smoke: Report from a Workshop on Effects and Exposure Levels. R. Rylander, Y. Peterson and M.C. Snella (eds.). European Journal of Respiratory Diseases, Supplement No. 133, Vol. 65, 121-126, 1984.
4. He, Y., et al., "Women's Passive Smoking and Coronary Heart Disease," Chung Hua Yu Fang I Hsueh Tsa Chih 23(1): 19-22, 1989.
5. Helsing, K.J., Sandler, D.P., Comstock, G.W. and Chee, E., "Heart Disease Mortality in Nonsmokers Living With Smokers," American Journal of Epidemiology 127(5): 915-922, 1988.
6. Hirayama, T., "Lung Cancer in Japan: Effects of Nutrition and Passive Smoking." In: Lung Cancer: Causes and Prevention. M. Mizell and P. Correa (eds.). New York, Verlag Chemie International, Chapter 14, 175-195, 1984.
7. Hole, D.J., Gillis, C.R., Chopra, C. and Hawthorne, V.M., "Passive Smoking and Cardiorespiratory Health in a General Population in the West of Scotland," British Medical Journal 299: 423-427, 1989.
8. Humble, C., Croft, J., Gerber, A., Casper, M., Hames, C.G. and Tyroler, H.A., "Passive Smoking and 20-Year Cardiovascular Disease Mortality among Nonsmoking Wives, Evans County, Georgia," American Journal of Public Health 80(5): 599-601, 1990.

10381016

9. Lee, P.N., Chamberlain, J. and Alderson, M.R., "Relationship of Passive Smoking to Risk of Lung Cancer and Other Smoking-Associated Diseases," British Journal of Cancer 54: 97-105, 1986.
10. Martin, M.J., Hunt, S.C. and Williams, R.R., "Increased Incidence of Heart Attacks in Nonsmoking Women Married to Smokers," Presented at the Annual Meeting of the American Public Health Association, Abstract, 1986.
11. Palmer, J.R., Rosenberg, L. and Shapiro, S., "Passive Smoking and Myocardial Infarction in Women," Abstract, CVD Epidemiology Newsletter No. 43, 29, Winter 1988.
12. Sandler, D.P., Comstock, G.W., Helsing, K.J. and Shore, D.L., "Deaths from All Causes in Non-Smokers Who Lived with Smokers," American Journal of Public Health 79(2): 163-167, 1989.
13. Svendsen, K.H., Kuller, L.H., Martin, M.J. and Ockene, J.K., "Effects of Passive Smoking in the Multiple Risk Factor Intervention Trial," American Journal of Epidemiology 126(5): 783-795, 1987.
14. Wells, A.J., "An Estimate of Adult Mortality in the United States from Passive Smoking," Environment International 14(3): 249-265, 1988.
15. Kawachi, I., Pearce, N.E. and Jackson, R.T., "Deaths from Lung Cancer and Ischaemic Heart Disease Due to Passive Smoking in New Zealand," New Zealand Medical Journal 102(871): 337-340, 1989.
16. Kristensen, T.S., "Cardiovascular Diseases and the Work Environment. A Critical Review of the Epidemiologic Literature on Chemical Factors," Scand. J. Work Environ. Health 15: 245-264, 1989.
17. Glantz, S.A. and Parmley, W.W., "Passive Smoking and Heart Disease: Epidemiology, Physiology, and Biochemistry," Circulation 83(1): 1-12, 1991.
18. U.S. Department of Health and Human Services, The Health Consequences of Involuntary Smoking: A Report of the Surgeon General. Publication No. DHHS (CDC) 87-8398, Washington, D.C., U.S. Government Printing Office, 1986.
19. Committee on Passive Smoking, Board on Environmental Studies and Toxicology, National Research Council, National Academy of Sciences, Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects. Washington, D.C., National

10381016

Academy Press, 1986.

20. Wexler, L.M., "Environmental Tobacco Smoke and Cardiovascular Disease: A Critique of the Epidemiological Literature and Recommendations for Future Research." In: Environmental Tobacco Smoke: Proceedings of the International Symposium at McGill University 1989. D.J. Ecobichon and J.M. Wu (eds.). Lexington, Mass., Lexington Books, D.C. Heath and Company, Chapter 8, 139-152, 1990.
21. Weetman, D.F. and Munby, J., "Environmental Tobacco Smoke (ETS) and Cardiovascular Disease." In: Indoor Air Quality and Ventilation. F. Lunau and G.L. Reynolds (eds.). London, Selper Ltd., 211-216, 1990.
22. Thiery, J. and Cremer, P., "Coronary Heart Disease and Involuntary Smoking," Paper presented at: Toxicology Forum (Session on "Environmental Tobacco Smoke: Science and Meta-Science"), Budapest, Hungary, June 19, 1990.
23. Armitage, A.K., "Environmental Tobacco Smoke and Coronary Heart Disease." In: Other People's Tobacco Smoke. A.K. Armitage (ed.). Beverly, E. Yorks, U.K., Galen Press, Chapter 7, 109-116, 1991.
24. McMurray, R.G., Hicks, L.L. and Thompson, D.L., "The Effects of Passive Inhalation of Cigarette Smoke on Exercise Performance," European Journal of Applied Physiology 54(2): 196-200, 1985.
25. Aronow, W.S., "Effect of Passive Smoking on Angina Pectoris," New England Journal of Medicine 299(1): 21-24, 1978.
26. Khalfen, E.Sh. and Klochkov, V.A., "Effect of 'Passive' Smoking on the Physical Load Tolerance of Coronary Heart Disease Patients," Ter. Arkh. 5: 112-115, 1987. [Uncertified translation]
27. Sinzinger, H. and Kefalides, A., "Passive Smoking Severely Decreases Platelet Sensitivity to Antiaggregatory Prostaglandins," Letter, The Lancet II, pp. 392-393, August 14, 1982.
28. Burghuber, O.C., Punzengruber, Ch., Sinzinger, H., Haber, P. and Silberbauer, K., "Platelet Sensitivity to Prostacyclin in Smokers and Non-smokers," Chest 90(1): 34-38, 1986.
29. Sinzinger, H. and Virgolini, I., "Are Passive Smokers at Greater Risk of Thrombosis?" Wiener Klinische Wochenschrift 20: 649-698, 1989.

10381016

2025500518

30. Davis, J.W., Shelton, L., Watanabe, I.S. and Arnold, J., "Passive Smoking Affects Endothelium and Platelets," Arach. Intern. Med. 149: 386-389, 1989.
31. Moskowitz, W.B., Mosteller, M., Schiekern, R.M., Bossano, R., Hewitt, J.K., Bodurtha, J.N. and Segrest, J.P., "Lipoprotein and Oxygen Transport Alterations in Passive Smoking Preadolescent Children: The MCV Twin Study," Circulation 81(2): 586-592, 1990.
32. Pomrehn, P., Hollarbush, J., Clarke, W. and Lauer, R., "Children's HDL--chol: The Effects of Tobacco; Smoking, Smokeless and Parental Smoking," Presented at the 30th Annual Conference on Cardiovascular Disease Epidemiology, Abstract, Circulation 81(2): 720, 1990.
33. Gvozdjakova, A., Bada, V., Sany, L., Kucharska, J., Kruty, F., Bozek, P. Trstansky, L. and Gvozdjak, J., "Smoke Cardiomyopathy: Disturbance of Oxidative Processes in Myocardial Mitochondria," Cardiovascular Research 18: 229-232, 1984.
34. Gvozdjakova, A., Kucharska, J., Sany, L., Bada, V., Bozek, P. and Gvozdjak, T., "Effect of Smoking on the Cytochrome and Oxidase System of the Myocardium," Bratisl. lek. Listy 83: 10-15, 1985.
35. Gvozdjak, J., Gvozdjakova, A., Kucharska, J. and Bada, V., "The Effect of Smoking on Myocardial Metabolism," Czech. Med. 10(1): 47-53, 1987.

PARENTAL SMOKING AND CHILDHOOD RESPIRATORY DISEASE/SYMPTOMS

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PARENTAL SMOKING

Perhaps no claim regarding environmental tobacco smoke (ETS) is as capable of provoking strong feelings as the charge that parents who smoke may compromise the health of their children. While the issue of parental smoking is laden with emotion, the scientific basis for the claim is difficult to interpret. None of the studies that have reported an association between parental smoking and a child's increased risk of developing respiratory infections or symptoms have actually measured exposure to ETS. Virtually all of the studies have failed to control for cross-infections in the home and other important confounding factors. Studies that have controlled for such factors have frequently reported no significant increased risk of respiratory disease in the children of smoking parents.¹⁻¹⁷

The studies on parental smoking, each with a different sample size, data collection method and analysis, tend to yield factually incompatible and contrary conclusions. For instance, although certain studies and reviews have reported adverse findings,¹⁸⁻⁴² others have observed no significant relationship between parental smoking and respiratory illness in children.^{5,6,8,43-53} After a five-year study of over 400 children, for example, Dutch researchers concluded there was "no evidence" that parental smoking had an appreciable effect on respiratory symptoms in school children.⁴⁹ A similar conclusion was reached by a group of U.S. researchers, including a critic of smoking, who found "no significant relation" between parental smoking and

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respiratory symptoms in a study of nearly 400 families with 816 children in three cities.⁴³

In 1988, investigators re-examined thirty studies on ETS exposures among children and evaluated the studies for their scientific validity.⁵⁴ They noted that while several studies had reported a statistically significant relationship between ETS exposure and respiratory illness in children, "most studies had significant design problems that prevent reliance on their conclusions." The authors concluded that "many questions remain, and future studies should consider important methodological standards to determine more accurately the effect of passive smoking on child health." In 1990, another group of researchers examined the existing literature on ETS and respiratory health.⁵⁵ Although critical of ETS, they concluded that "[f]urther studies of health effects are needed; such studies will require improved methods of exposure assessment, as well as better understanding of dose-response relationships."

The studies on parental smoking have relied solely on questionnaires to obtain exposure data.⁵⁵ Reliance on questionnaires casts doubt on the findings of these studies for several reasons. First, it has been noted that even "slight changes" in the way the questions were phrased could result "in substantial differences in the type of responses one obtains."²⁸ Secondly, one study observed that there was a significant difference in the respiratory symptoms reported depending on which

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parent completed the questionnaire.³⁸ It has been reported that mothers are more likely than fathers to report chronic respiratory problems in their children and that asymptomatic mothers are less likely than symptomatic mothers to report symptoms in their children.⁵⁵ It has been suggested that "[t]hese potential biases must be evaluated in epidemiologic studies."⁵⁵

In conclusion, although a number of studies have been conducted on parental smoking and childhood respiratory health, the results of these studies are inconsistent and are limited by the methodology employed in each study. Questionnaires are not an accurate method of determining the actual exposure of ETS a child receives from his/her smoking parent. Many studies report no relationship for parental smoking, particularly when confounding factors such as diet, home dampness or cross-infection in and outside the home are considered. Childhood respiratory illness appears to be influenced by many different social, familial, and environmental factors. To isolate parental smoking as a cause is scientifically unjustified.

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REFERENCES

1. Anderson, L., et al., "Day Care Center Attendance and Hospitalization for Lower Respiratory Tract Illness," Pediatrics 82(3): 300-308, 1988.
2. Berwick, M., et al., "Lower Respiratory Symptoms in Children Exposed to Nitrogen Dioxide From Unvented Combustion Sources," Environment International 15: 369-373, 1989.
3. Berglund, B., et al., "Radon, Passive Smoking, Particulates and Housing Epidemiology," Indoor Air 2: 255-260, 1984.
4. Brunekreef, B., et al., "Home Dampness and Respiratory Morbidity in Children," Am. Rev. Respir. Dis 140: 1363-1367, 1989.
5. Harrington, W. and Krupnick, Alan J., "Short-Term Nitrogen Dioxide Exposure and Acute Respiratory Disease in Children," JAPCA 35: 1061-1087, 1985.
6. Holma, B. and Winding, O., "Housing, Hygiene, and Health: A Study in Old Residential Areas in Copenhagen," Archives of Environmental Health 32(2): 86-93, 1977.
7. Kerigan, A., et al., "A Three-Year Cohort Study of the Role of Environmental Factors in the Respiratory Health of Children

2025500524

- in Hamilton, Ontario," Am. Rev. Respir. Dis. 133: 987-993, 1986.
8. Martin, C., et al., "Housing Conditions and Ill Health, " British Medical Journal 294: 1987.
9. Melia, R.J.W., et al., "Association Between Gas Cooking and Respiratory Disease in Children," British Medical Journal, 149-152, 1977.
10. Melia, R.J.W., et al., "The Relation Between Respiratory Illness in Primary Schoolchildren and the Use of Gas for Cooking, I- Results From a National Survey," International Journal of Epidemiology 8(4): 333-338, 1979.
11. National Institutes of Health, Public Health Service, U.S. Department of Health and Human Services, May 1-3, 1983, "Report of Workshop on Respiratory Effects of Involuntary Smoke Exposure: Epidemiologic Studies"
12. Mitchell, E., et al., "Socioeconomic Status in Childhood Asthma," International Journal of Epidemiology 18(4): 888-890, 1989.
13. Nordvall, S.L., et al., "Sensitization of Children in the Stockholm Area to House Dust Mites," Acta Paediatr Scan 77(5): 716-720, 1988.

2025500525

14. Osborne, J.S., "Health Effects of Heating With Wood: Chest Illness in Young Children and Indoor Heating with Woodburning Stoves," *The Human Equation: Health and Comfort, Indoor Air Quality '89*, April 17-20, 1989, San Diego, CA.
15. Platt, S., et al., "Damp Housing, Mould Growth, and Symptomatic Health State," *BMJ* 298: 1673-1678, 1989.
16. Pope, C., "Respiratory Disease Associated with Community Air Pollution and a Steel Mill, Utah Valley," *AJPH* 79(5): 623-628, 1989.
17. Strachan, D. and Elton, R., "Relationship Between Respiratory Morbidity in Children and the Home Environment," *Family Practice* 3(3): 137-142, 1986.
18. Committee on Passive Smoking, Board on Environmental Studies and Toxicology, National Research Council, Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects (Washington: National Academy Press, 1986).
19. U.S. Department of Health and Human Services, The Health Consequences of Involuntary Smoking: A Report of the Surgeon General (U.S. DHHS: Washington, 1986).

2025500526

20. Bland, M., et al., "Effect of Children's and Parents' Smoking on Respiratory Symptoms," Arch Dis Child 53(2): 100-105, 1978.
21. Bonham, G. and R. Wilson, "Children's Health in Families with Cigarette Smokers," Am Public Health 71(3): 290-293, 1981.
22. Burchfiel, C., et al., "Passive Smoking in Childhood: Respiratory Conditions and Pulmonary Function in Tecumseh, Michigan," Am Rev Respir Dis 133(6): 966-73, 1986.
23. Cameron, P. and D. Robertson, "Effect on Home Environment Tobacco Smoke on Family Health," J Appl Psychol 57(2): 142-147, 1973.
24. Chen, Y., "Synergistic Effect of Passive Smoking and Artificial Feeding on Hospitalization for Respiratory Illness in Early Childhood," Chest 95: 1004-07, 1989.
25. Colley, J., "Respiratory Symptoms in Children and Parental Smoking and Phlegm Production," Br Med J II: 201-204, 1974.
26. Colley, J., et al., "Influence of Passive Smoking and Parental Phlegm on Pneumonia and Bronchitis in Early Childhood," Lancet II: 1031-1034, 1974.

2025500527

27. Dockery, D., et al., "Effects of Inhalable Particles on Respiratory Health of Children," Am Rev Respir Dis 139: 587-594, 1989.
28. Ekwo, E., et al., "Relationship of Parental Smoking and Gas Cooking to Respiratory Disease in Children," Chest 84(6): 662-668, 1983.
29. Fergusson, D., et al., "Parental Smoking and Lower Respiratory Illness in the First Three Years of Life," J Epidemiol Community Health 35(3): 180-184, 1981.
30. Fergusson, D., et al., "Parental Smoking and Respiratory Illness During Early Childhood," Ped Pul 1(2): 99-106, 1985.
31. Ferris, B., et al., "The Six-City Study: Examples of Problems in Analysis of Data," Environ Health Perspect 52: 115-123, 1983.
32. Gortmaker, S., et al., "Parental Smoking and the Risk of Childhood Asthma," Am J Public Health 72(6): 574-579, 1982.
33. Harlap, S. and A. Davies, "Infant Admissions to Hospital and Maternal Smoking," Lancet I: 529-532, 1974.

2025500528

34. Kraemer, M., et al., "Risk Factors for Persistent middle Ear Effusions: Otitis Media, Catarrh, Cigarette Smoke Exposure, and Atopy," JAMA 249(8): 1022-1025, 1983.
35. Murray, A., and B. Morrison, "Passive Smoking and the Seasonal Difference of Severity of Asthma in Children," Chest 94(4): 701-708, 1988.
36. Neuspiel, D., et al., "Parental Smoking and Post-Infancy Wheezing in Children: A Prospective Cohort Study," AJPH 79(2): 168-171, 1989.
37. Ogston, S., et al., "Association of Infant Alimentary and Respiratory Illness with Parental Smoking and Other Environmental Factors," J Epidemiol Commun Health 41(1): 21-25, 1987.
38. Schenker, M., et al., "Risk Factors for Childhood Respiratory Disease: The Effect of Host Factors and Home Environmental Exposures," Am Rev Respir Dis 128: 1038-1043, 1983.
39. Somerville, S., et al., "Passive Smoking and Respiratory Conditions in Primary School Children," J Epidemiol Commun Health 42(2): 105-110, 1988.

2025500529

40. Strachan, D., et al., "Passive Smoking, Salivary Cotinine Concentrations, and Middle Ear Effusion in 7 Year Old Children," BMJ 298: 1549-1552, 1989.
41. Tsimoyianis, G., et al., "Reduction in Pulmonary Function and Increased Frequency of Cough Associated With Passive Smoking in Teenage Athletes," Pediatrics 80(1): 32-36, 1987.
42. Ware, J., et al., "Passive Smoking, Gas Cooking, and Respiratory Health of Children Living in Six Cities," Am Rev Respir Dis 129: 366-374, 1984.
43. Schilling, R., et al., "Lung Function, Respiratory Disease, and Smoking in Families," Am J Epidemiol 106(4): 274-283, 1977.
44. Camacho, E., et al., "Pulmonary Symptoms and Pulmonary Functional Tests Among Children in Relation to the Area of Residence," Eur Respir Dis 63(2): 165-166, 1982.
45. Binder, R., et al., "Importance of the Indoor Environment in Air Pollution Exposure," Arch Environ Health 31(6): 277-279, 1976.
46. Bouhuys, A., "Lung Diseases in Rural and Urban Communities," Report Sponsored by the Division of Lung Diseases, National

2025500530

Heart, Lung and Blood Institute, U.S. National Institutes of Health, pp. 77-89, June 10, 1977.

47. Gardner, G., et al., "Effects of Social and Family Factors on Viral Respiratory Infection and Illness in the First Year of Life," J Epidemiol Community Health 38: 42-48, 1984.
48. Kallail, K., et al., "Passive Smoking and Middle Ear Problems in Kansas Public School Children," J Commun Disord 20: 187-96, 1987.
49. Kerrebijn, J., et al., "Chronic Nonspecific Respiratory Disease in Children, A Five Year Follow-Up Study," Acta Paediatr Scand, Suppl. 261: 11-72, 1977.
50. Lebowitz, M. and B. Burrows, "Respiratory Symptoms Related to Smoking Habits of Family Adults," Chest 69(1): 48-50, 1976.
51. Love, G., et al., "The Incidence and Severity of Acute Respiratory Illness in Families Exposed to Different Levels of Air Pollution, New York Metropolitan Area, 1971-72," Arch Environ Health 36(2): 66-73, 1981.
52. Salzman, M., et al., "Passive Smoking and Croup," Arch Otolaryngol Head Neck Surg 113: 866-868, 1987.

2025500531

53. Shy, C., et al., "The Chattanooga School Children Study: Effects of Community Exposure to Nitrogen Dioxide. II. Incidence of Acute Respiratory Illness," J Air Pollut Control Assoc 20(9): 582-588, 1970.
54. Rubin, D. and K. Damus, "The Relationship Between Passive Smoking and Child Health: Methodologic Criteria Applied to Prior Studies," Yale J Bio Med 61(5): 401-411, 1988.
55. Schenker, M.B. and Pocekay, D.E., "Environmental Tobacco Smoke: Assessment of Exposure and Effects on Respiratory Health" Problems in Resp. Care 3(2): 193-205, 1990.

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PARENTAL SMOKING AND CHILDRENS' LUNG FUNCTION

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LUNG FUNCTION IN CHILDREN

The studies that have investigated lung function in children and its possible relationship to environmental tobacco smoke exposure are presented in this section. To aid in the interpretation of this literature, definitions of the major lung function parameters are provided below.

Df: One of the most widely used measures of pulmonary function in adults and children is forced vital capacity and is represented in the literature as FVC. This term refers to the maximum volume of gas that a person can expire as forcefully and rapidly as possible from their lungs immediately following a maximal inspiration of air. When a person's ability to expire air forcefully and rapidly from their lungs (FVC) is compromised, this can possibly be an indication of chronic obstructive lung disease. Decreased FVC is common in restrictive diseases such as pulmonary fibrosis and in obstructive diseases such as emphysema and asthma.

Df: A second important measure of pulmonary function is the forced expiratory volume in one second, which is abbreviated as FEV1 in the literature. The FEV1 measure is simply the amount of air that is expired in the first second of the FVC maneuver. As with FVC, this parameter is useful in the assessment of airway obstruction. The two parameters, FVC and FEV1, are often used in a ratio to determine the percentage of a person's FVC that is expired in the first second of the maneuver. A FEV1/FVC ratio lower than 65% to 70% is characteristic of obstructive lung disease. On the other hand, subjects with restrictive lung disease will often show a normal or exaggerated FEV1/FVC value.

Df: Forced expiratory flow, known as FEF25%-75% is the average rate of flow of air during the middle half of an FEV maneuver. The FEF25%-75% is indicative of the status of the medium and small sized airways. Decreased values of FEF25%-75% are common in the early stages of obstructive lung disease. Low values of FEF25%-75% in combination with normal values of FVC and FEV1 are often indicative of early small airways abnormality. Reduced FEF25%-75% are sometimes seen in cases of severe restrictive disease as well.

All of these measures share a common problem: accurate assessment requires the full cooperation and maximal effort of the subjects under investigation. Accurate measures are sometimes

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therefore difficult to obtain, especially when the subjects are young children who do not fully comprehend the requirements being made of them in the pulmonary function tests. The studies are not consistent in the lung function parameters they measure, and there is also a lack of consistency among the results of the same function tests across studies. Following is a presentation of the major studies that have examined these lung function parameters in children. The investigators who have found associations between impaired lung function and ETS exposure are often uncertain of the clinical meanings of the small decreases observed in their studies. Therefore, it is not suprising that no definitive conclusions have been reached regarding ETS exposure and its possible association with lung function in children.

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REFERENCE

Ruppel, Gregg. Manual of pulmonary function testing: (Fourth edition). The C.V. Mosby Company, 1986, pp. 33-38.

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RESULTS OF SELECTED STUDIES: CHILDHOOD LUNG FUNCTION

STUDY	EFFECT ON FEV1, FEV.75	EFFECT ON FEF25-75%
Tager 1976	decrease	not reported
Tager 1979	none	decrease
Weiss 1980	none	decrease
Tager 1983	decrease 7%	none
O'Connor 1987	decrease 5-7%	decrease 14-15%
Ware 1984	decrease .6-.9%	not reported
Berkey 1986	decrease .85%	not reported
Hasselblad 1981	decrease .5-2%	not reported
Tashkin 1984	none	decrease 2.5%
Ekwo 1983	none	none
Vedal 1984	none	decrease 4%
Spinaci 1985	decrease	none
Chen 1986	decrease 3%	decrease 6%
Burchfiel 1986	decrease 4-5%	not reported
Yarnell 1979	decrease 3%	decrease 12%
Teculesco 1986	decrease 5%	not reported
Tsimoyianis 1987	not done	decrease
Lebowitz 1987	none	not done
Leeder 1976	not done	not done
Schilling 1977	none	not reported
Speizer 1980	none	not reported
Dodge 1982	none	not reported
Lebowitz 1984	none	not reported
Lebowitz 1984	not done	not done

Adapted from Witorsch 1989

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PARENTAL SMOKING AND COMPROMISED CHILDREN

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COMPROMISED CHILDREN

The literature on environmental tobacco smoke includes a body of research on asthma and the relationship between parental smoking and preexistent disease in children. While only a few studies have been conducted thus far on children with, for example, cystic fibrosis (a genetic disorder whereby lung passages often become blocked by abnormally behaving mucus), there have been numerous studies that have examined asthmatic children and the presence of smokers in the home. The results of the studies have been variable and are subject to the influences of many different confounders such as socioeconomic status, genetic determinants, damp housing, and gas cooking in the home. It is not suprising, therefore, that researchers are inconsistent in their interpretation of the available data on exposure to ETS and childhood asthma. Following is a presentation of the major studies that have examined a possible association of ETS with asthma in children. Also included are the studies available on children with cystic fibrosis.

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RESULTS OF SELECTED STUDIES: COMPROMISED CHILDREN

Leeder, et al., 1976

Reported that episodes of asthma in the first five years of life showed an association with parental history of asthma-wheeze and that there is little relationship between asthma in the first five years of life and other family, social, or environmental factors.

Fergusson, et al., 1985

Reported that maternal smoking increased the risk of lower respiratory infections/symptoms during the child's first two years of life, and that after two years this association seemed to disappear. Also reported that there was no increased risk of asthma or asthma attacks attributable to maternal smoking.

Horwood, et al., 1985

Reported that there was no evidence to suggest that the structure, practices (including parental smoking), or the dynamics of the family played a significant role in the development of childhood asthma.

Murray, et al., 1986

Reported that maternal smoking aggravated symptoms in asthmatic children.

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Anderson, et al., 1987

Reported that sex of child, mother's age at the child's birth, pneumonia, whooping cough, tonsillectomy, adenoidectomy, allergic rhinitis, eczema and periodic abdominal pain/vomiting attacks were associated with the development of childhood asthma.

• Evans, et al., 1987 •

Reported that parental smoking increased the number of emergency room visits of children with asthma. The lack of an association between parental smoking and symptoms in asthmatic children caused the authors to question the mechanism whereby parental smoking would increase ER visits.

• Toyoshima, et al., 1987

Reported that it was not clear whether parental smoking increased the incidence of asthmatic disease in children.

• Kershaw, 1987

The authors conceded that the association observed with parental smoking may reflect a relationship of smoking behaviour to a number of other social factors such as medical care utilization and maternal stress.

• Murray, et al., 1988

Reported that paternal smoking, including the number of cigarettes the father smoked at home, had no association with any test results. Maternal smoking in the "wet and cold" season was reported to increase the severity of the child's asthma. There was no association in the "warm and dry" season

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• Somerville, et al., 1988

and the severity of the child's asthma. The authors attribute this to increased ventilation in the "warm and dry" season.

Oldigs, et al., 1990

Reported a positive association between parental smoking and asthma in girls and a non-significant negative relation between parental smoking and asthma in boys.

Sherman, et al., 1990

Reported that in children with mild bronchial asthma one hour of passive smoke exposure did not cause airway obstruction or changes in bronchial responsiveness.

• Weitzman, et al., 1990

Neither bronchiolitis, eczema, croup, personal cigarette smoking, maternal smoking, paternal smoking, nor delivery complications bore an apparent relation to the development of childhood asthma.

• Rubin, 1990

The authors concede that the estimate of children's exposure to cigarette smoke is "crude", based on parent reporting of smoking during pregnancy.

Reported an association between parental smoking and the severity of cystic fibrosis in children. However, the authors conceded that it could not be ruled out that social, economic, or other factors determined both the smoking status of the household and the nutritional status of the children.

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Gilljam, et al., 1990

Reported that there was no statistical difference in clinical status or pulmonary function between children with cystic fibrosis from smoking and nonsmoking families. For patients with higher levels of physical activity, parental smoking appeared to matter less.

Young, et al., 1991

Reported that parental smoking may contribute to a higher level of airway responsiveness early in the child's life. The authors conceded that they did not report the actual amount of parental smoking due to the inaccuracies of parental reporting.

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PARENTAL SMOKING AND OTITIS MEDIA IN CHILDREN

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OTITIS MEDIA ("GLUE EAR")

In addition to claims that parental smoking affects the respiratory health of children, there are claims that exposure to parental smoking might increase the risk of otitis media (commonly known as "glue ear") in children. Otitis media is an inflammation of the inner ear that often leads to an accumulation of fluid in the inner ear canal. Otitis media often appears as a complication of various viral and bacterial infections, including measles. If left undetected, otitis media can lead to hearing loss and learning disabilities. Authors of studies examining this issue have not formulated a widely accepted mechanism for how ETS might increase the risk of otitis media in children. There are two theories that are proposed but have not been scientifically proven: 1) One theory is that ETS somehow chronically irritates the eustachian tube of the inner ear, leading to the inflammation; and 2) The second theory is that ETS potentially increases the risk of upper respiratory tract infections that spread to the inner ear. The results of the studies on this subject are variable and are subject to the same confounders that potentially bias the results of studies on other ETS related issues. While the science on this issue is controversial, the reported seriousness of otitis media makes investigators anxious to make recommendations for child safety. However, the studies on otitis media and parental smoking have not established a clear association.

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RESULTS OF SELECTED STUDIES ON OTITIS MEDIA

- | | |
|-----------------------------|--|
| / Said, et al., 1978 | Reported that number of tonsillectomies/adenoidec-tomies were related to the amount of parental smoking in the home |
| * Pukander, et al., 1985 | Reported that parental smoking in the home increased the risk of acute otitis media and that breast-feeding seemed to have a protective effect |
| Kallail, et al., 1987 | Reported that parental smoking was not associated with the occurrence of otitis media |
| Zielhuis, 1989 | Reported that parental smoking was not related to an increased risk of otitis media |
| * Strachan, 1990 | Reported that parental smoking was an important determinant of middle-ear underpressure and effusion |
| Strachan, 1989 | Reported that approximately one-third of the cases of middle ear effusion in their subjects were attributable to passive smoking |
| Taninio, et al., 1988 | Reported that parental smoking was more prevalent among the subjects with recurrent otitis media |
| * Kraemer et al, 1983 | Reported that parental smoking, atopy, and catarrh posed the greatest risk to children of developing persistent middle-ear effusions when present together in the same child |

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- Pukander, et al., 1990
Reported that maternal smoking increased the risk of acute otitis media in infants and especially of recurrent attacks
- Vinther, et al., 1982
Reported that there were no effects of parental smoking on the frequency of otitis media in children
- Moorhead, 1985
Reported that otitis media was found to be related to parental smoking in this general practice study
- Black, 1985
Reported that parental smoking increased a child's risk of undergoing surgery for otitis media
- Fleming, et al., 1987
Reported that full time day-care attendance increased the risk of ear infections (odds ratio = 3.8)

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ETS AND ADULT RESPIRATORY DISEASE/SYMPTOMS

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ADULT RESPIRATORY DISEASE

Several studies have examined respiratory disease and symptoms and their possible association with exposure to environmental tobacco smoke in adults. The studies that examined respiratory disease and symptoms in adults are contained in this section. For additional studies on adults, see the "compromised individuals" and "lung function" sections.

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RESULTS OF SELECTED STUDIES: ETS AND ADULT RESPIRATORY HEALTH

Lee, 1986

Passive smoking was not associated with an increased risk of chronic bronchitis in the nonsmoker.

Koo, et al., 1988

Reported an association between respiratory symptoms in the mothers and the same symptoms in their children. Indicates that cross-infection is an important confounder of studies on parental smoking and childhood respiratory health.

Hole, et al., 1989

Reported an association between passive smoking and adverse cardiorespiratory symptoms in adult nonsmokers. None of the associations, however, were significant.

Koo, et al., 1990

With the exception of smoking by the father and the children's NO₂ levels, no association was found between smoking at home and NO₂ levels.

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ETS AND ADULT LUNG FUNCTION

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LUNG FUNCTION IN ADULTS

The studies that have investigated lung function in adults and its possible relationship to environmental tobacco smoke exposure are presented in this section. To aid in the interpretation of this literature, definitions of the major lung function parameters are provided below.

Df: One of the most widely used measures of pulmonary function in adults and children is forced vital capacity and is represented in the literature as FVC. This term refers to the maximum volume of gas that a person can expire as forcefully and rapidly as possible from their lungs immediately following a maximal inspiration of air. When a person's ability to expire air forcefully and rapidly from their lungs (FVC) is compromised, this can possibly be an indication of chronic obstructive lung disease. Decreased FVC is common in restrictive diseases such as pulmonary fibrosis and in obstructive diseases such as emphysema and asthma.

Df: A second important measure of pulmonary function is the forced expiratory volume in one second, which is abbreviated as FEV1 in the literature. The FEV1 measure is simply the amount of air that is expired in the first second of the FVC maneuver. As with FVC, this parameter is useful in the assessment of airway obstruction. The two parameters, FVC and FEV1, are often used in a ratio to determine the percentage of a person's FVC that is expired in the first second of the maneuver. A FEV1/FVC ratio lower than 65% to 70% is characteristic of obstructive lung disease. On the other hand, subjects with restrictive lung disease will often show a normal or exaggerated FEV1/FVC value.

Df: Forced expiratory flow, known as FEF25%-75%, is the average rate of flow of air during the middle half of an FEV maneuver. The FEF25%-75% is indicative of the status of the medium and small sized airways. Decreased values of FEF25%-75% are common in the early stages of obstructive lung disease. Low values of FEF25%-75% in combination with normal values of FVC and FEV1 are often indicative of early small airways abnormality. Reduced FEF25%-75% are sometimes seen in cases of severe restrictive disease as well.

All of these measures share a common problem: accurate assessment requires the full cooperation and maximal effort of the subjects under investigation. Accurate measures are sometimes

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therefore difficult to obtain. The studies are not consistent in the lung function parameters they measure, and there is also a lack of consistency among the results of the same function tests across studies. Following is a presentation of the major studies that have examined these lung function parameters in adults. The investigators who have found associations between impaired lung function and ETS exposure are often uncertain of the clinical meanings of the small decreases observed in their studies. Therefore, it is not suprising that no definitive conclusions have been reached regarding ETS exposure and its possible association with lung function in adults.

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REFERENCE

Ruppel, Gregg. Manual of pulmonary function testing (Fourth edition). The C.V. Mosby Company, 1986, pp. 33-38.

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RESULTS OF SELECTED STUDIES: ETS AND ADULT LUNG FUNCTION

Bouhuys, et al., 1978

The authors reported no associations between smoking in the home and increased symptoms or lung function loss among nonsmokers living in the same households.

Shephard, et al., 1979

The authors raise the possibility that subjective reporting of symptoms could have been "suggested" by the odor of the cigarette smoke.

White, et al., 1980

This study has received numerous criticisms.

Comstock, et al., 1981

Passive smoking in the home was not associated with the prevalence of respiratory symptoms and was only "suggestively associated" with impaired ventilatory function.

Kauffmann, et al., 1983

Opposite trends in FEV1 and FEF25-75 were found in men passively exposed to tobacco smoke, and the differences observed in women were slight and not statistically significant.

Jones, et al., 1983

The use of cooking fuels was found to be associated with impaired ventilatory function in a group of nonsmoking women.

Kentner, et al., 1984

Passive inhalation of tobacco smoke at home or the workplace was found not to be associated with impaired lung function in healthy nonsmokers.

Lebowitz, et al., 1985

Reported no direct association between ETS and lung function parameters in adult nonsmokers.

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Hosein, et al., 1986

The use of gas stoves was found to be associated with impaired lung function in women. It was reported that passive smoking in households where gas stoves were used appeared to have no effect on lung function values.

Masi, et al., 1988

The authors concede that their use of multiple tests of significance (involving both exposure and response measurements) are likely to have resulted in some associations achieving statistical significance by chance.

Kalandidi, et al., 1990

Assessment of exposure was based solely on the husband's smoking habit in terms of amount (daily), amount (total), and duration.

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ETS AND COMPROMISED ADULTS

COMPROMISED ADULTS

The literature on environmental tobacco smoke includes a body of research on asthmatic adults. Studies have been conducted in order to attempt to determine whether there is a relationship between passive exposure to ETS and the development of asthma or the exacerbation of existing asthma in adults. The studies are varied in their results, and accordingly, no definitive conclusions have been reached by investigators. Following are the studies that examine ETS and its possible relation to asthma in adults.

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COMMENTS ON SELECTED STUDIES: ETS AND COMPROMISED ADULTS

Stahle, et al., 1978

The authors suggest that tobacco smoke exposure might trigger asthma attacks by means of an allergic reaction.

Shephard, et al., 1979

Reported that asthmatic subjects did not appear to have an unusual sensitivity to tobacco smoke exposure.

Dahms, et al., 1981

Five of the ten subjects specifically reported sensitivity to tobacco smoke before their inclusion in this study.

Ing, et al., 1983

This study investigated only six subjects.

Romer, et al., 1983

The authors concede that the small subject population of this study indicates that the results must be taken with caution.

Knight, et al., 1985

Only six subjects were studied.

Wiedemann, et al., 1986

The authors report that passive smoking presents no acute respiratory risk to young asymptomatic asthmatic patients.

Stankus, et al., 1988

Only 21 subjects were included and all had complained of respiratory symptoms upon previous exposure to environmental tobacco smoke.

Bailey, et al., 1990

No relationship was observed between passive smoking and pulmonary function of asthmatic subjects.

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CONFOUNDERS

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CONFOUNDERS

Studies on parental smoking and childhood respiratory disease rarely address confounding variables. Confounding variables are factors that can create a "false" association between two elements by being associated with one or both of them. For example, factor X (socioeconomic status) may be associated with both factor Y (parental smoking) and factor Z (childhood respiratory disease). When factor X is not controlled for in epidemiological studies of the possible association between factor Y and factor Z, a false association may appear between factors Y and Z. Therefore, it is vital that epidemiologists control for confounding variables when conducting studies such as those on parental smoking. The possible confounding variables associated with parental smoking and childhood respiratory disease can be grouped into four major categories: (1) household heating and cooking sources; (2) outdoor air pollution; (3) organic substances; and (4) demographic, medical and socioeconomic factors.

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Household heating and cooking sources

Children living in households with gas stoves have been reported to have a greater history of respiratory illness before the age of two and small but significantly lower levels of FEV₁ and FVC corrected for height¹ (FEV₁ and FVC are standard measurements of lung capacity and function). Similarly, exposure of children to gas cooking in the first two years of life has been associated with an increased risk of hospitalization for respiratory illness². There are reported associations of gas stove use with daily peak flow in asthmatic, normal, and allergic subjects.³

Oxides of nitrogen (NOx) arising from the use of gas stoves for cooking were proposed to be related to a reported increase in cough, "colds going to the chest," and bronchitis in a study of 5,758 English and Scottish children aged six to eleven years⁴. A number of other confounders were controlled for in this study, including "age, social class, latitude, population density, family size, overcrowding, outdoor levels of smoke and sulphur dioxide and types of fuel used for heating." One group of researchers reported similar results for a five-year longitudinal study of 4827 boys and girls, ages five to ten years. This reported association was independent of age, sex, social class, number of cigarette smokers in the home, and latitude, and was only found in urban areas.⁵

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Use of unvented kerosene heaters, which release nitrogen dioxide (NO_2) into the indoor environment, was associated with significantly more days of acute respiratory illness in exposed children⁶. In this study, there was no difference in the number of cigarettes smoked daily in the homes of exposed versus unexposed children. NO_2 exposure was also reported to be associated with a risk of reporting lower respiratory symptoms in children under the age of seven⁷.

One study reported increased proportions of chest illnesses and hospitalizations for chest illness before age two in young children living in homes heated by wood-burning stoves. Medical histories, sociodemographic factors, or exposure to other pollutant sources did not account for the reported association⁸.

In another report, hot water heating systems were reported to have a large effect on lung function in children, when compared to the use of forced air heating and air conditioning systems⁹.

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REFERENCES

1. Speizer, F., et al., "Respiratory Disease Rates and Pulmonary Function in Children Associated with NO₂ Exposure," American Review of Respiratory Disease, 121(1): 3-10, 1980.
2. Ekwo, E.E., et al., "Relationship of Parental Smoking and Gas Cooking to Respiratory Disease in Children," Chest 84(6): 662-668.
3. Lebowitz, M.D., "The Effects of Environmental Tobacco Smoke Exposure and Gas Stoves on Daily Peak Flow Rates in Asthmatic and Non-Asthmatic Families," ETS - Environmental Tobacco Smoke: Report from a Workshop on Effects and Exposure Levels, eds., R. Rylander, et al., European Journal of Respiratory Diseases Suppl., 133(65): 90-97, 1984.
4. Melia, R.J.W., et al., "Association Between Gas Cooking and Respiratory Disease in Children," British Medical Journal, 149-152, 1977.
5. Melia, R.J.W., et al., "The Relation Between Respiratory Illness in Primary Schoolchildren and the Use of Gas for Cooking, I - Results From a National Survey," International Journal of Epidemiology, 8(4): 333-338, 1979.

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6. Berglund, B., et al., "Radon, Passive Smoking, Particulates and Housing Epidemiology," Indoor Air 2: 255-260, 1984.
7. Berwick, M., et al., "Lower Respiratory Symptoms in Children Exposed to Nitrogen Dioxide From Unvented Combustion Sources," Environment International 15: 369-373, 1989.
8. Osborne, J.S. and R.E. Honicky, "Health Effects of Heating With Wood: Chest Illness in Young Children and Indoor Heating with Woodburning Stoves," The Human Equation: Health and Comfort, ASHRAE/SOEH Indoor Air Quality '89, April 17-20, 1989, San Diego, CA.
9. Hosein, H.R., et al., "The Effect of Domestic Factors on Respiratory Symptoms and FEV₁," International Journal of Epidemiology 18(2): 390-396, 1987.

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Outdoor air pollution

Outdoor air pollutants have been identified as a confounder in several studies. In one study, acute respiratory disease incidence was reported to be positively associated with higher ambient sulfate levels¹.

A group of researchers examined the importance of indoor and outdoor environmental factors (parental smoking, gas cooking, suspended particulates and sulfur dioxide) in the respiratory health of seven- to ten-year-old Canadian children. The researchers were unable to identify any effects of parental smoking or gas cooking because the prevalence of these variables was highest in an industrial area of high particulate pollution².

One researcher has reported a strong association between respiratory illness and particulate pollution in children living in a study site which experiences relatively high levels of particulate pollution³.

A study comparing Israeli children living in a polluted industrial town versus those living in an unpolluted area reported that chronic respiratory symptoms and most pulmonary diseases were significantly more common among those children from the polluted town⁴.

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REFERENCES

1. Harrington, W. and Krupnick, Alan J., "Short-Term Nitrogen Dioxide Exposure and Acute Respiratory Disease in Children," JAPCA 35: 1061-1087, 1985.
2. Kerigan, A., et al., "A Three-Year Cohort Study of the Role of Environmental Factors in the Respiratory Health of children in Hamilton, Ontario," American Review of Respiratory Disease, 133: 987-993, 1986.
3. Pope, C., "Respiratory Disease Associated with Community Air Pollution and a Steel Mill, Utah Valley," AJPH, 79(5): 623-628, 1989.
4. Goren, A.I. and S. Hellmann, "Prevalence of Respiratory Symptoms and Diseases in Schoolchildren Living in a Polluted and in a Low Polluted Area in Israel," Environmental Research 45: 28-37, 1987.

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Organic substances

The relevance of home dampness in the etiology of respiratory symptoms in children is supported by current research which links dampness with the presence of molds, dust mites, fungi and other allergenic microbes.

In one study, odds ratios of 1.23 and 2.16 were reported for home dampness after adjustment for several factors, including maternal smoking, in a cohort study of 4,625 eight- to twelve-year-old children living in six United States cities¹. The authors reported odds ratios for molds of 1.27 to 2.12 after adjustment for maternal smoking and several other factors.

Another study reported higher rates of respiratory symptoms and symptoms of infection and stress among children living in damp houses. The presence of "fungal mould" was also reported to be related to higher rates of respiratory symptoms, independent of smoking in the household². In another study, the growth of fungi and molds in the home was directly related to respiratory symptoms and sensitization to common allergens in children³.

Researchers have reported that children living in damp and moldy dwellings had a greater prevalence of respiratory symptoms and headache and fever than those living in dry homes. The authors reported a dose-response relationship with increasing

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numbers of symptoms reported in dwellings with higher severity of dampness and mold. All these differences persisted after controlling for possible confounding factors such as household income, cigarette smoking, unemployment, and overcrowding⁴.

Atopic sensitization of children to house dust mites was reported to be related to home dampness⁵.

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REFERENCES

1. Brunekreef, B., et al., "Home Dampness and Respiratory Morbidity in Children," American Review of Respiratory Diseases 140: 1363-1367, 1989.
2. Martin, C., et al., "Housing Conditions and Ill Health," British Medical Journal, 294: 1987.
3. Ownby, D. and J. McCullough, "Passive Exposure to Cigarette Smoke Does Not Increase Allergic Sensitization in Children," J Allergy Clin Immunol 82(4): 634-638, 1988.
4. Platt, S., et al., "Damp Housing, Mould Growth, and Symptomatic Health State," British Medical Journal, 298: 1673-1678, 1989.
5. Nordvall, S.L., et al., "Sensitization of Children in the Stockholm Area to House Dust Mites," Acta Paediatr Scan, 77(5): 716-720, 1988.

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Demographic, medical and socioeconomic factors

Low socioeconomic status has been associated with an increased incidence of respiratory complications¹. Factors related to lower socioeconomic status include: inadequate medical care, poor nutrition, poor outdoor air quality, increased parental coughing, higher gas stove usage, frequent change of address, and lower per capita living space. In a study of 1,050 European children aged eight and nine years, lifetime and current prevalence of wheeze were both significantly higher in children from low socioeconomic status².

Watkins, et al., (1986) reported high consultation rates for respiratory illness in children whose fathers were in manual occupations. This association was not explained by crowded home conditions or parental smoking³. Gardner, et al., (1984) reported significantly higher rates of lower respiratory disease in infants of low socioeconomic status⁴.

Cross-infection also plays a role in the incidence of children's respiratory disease. For instance, in a 1988 paper, Koo, et al., reported that among Japanese and Hong Kong Chinese women, there was a highly significant correlation between the frequency of maternal respiratory illness and the frequency of respiratory illness in her children⁵.

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Cross-infection may be relevant to the reports of associations between day care attendance and respiratory illness. Anderson, et al., (1988) reported that care outside the home (day care) is an important factor for acquiring lower respiratory tract illness and infectious diseases in children under two years of age⁶. Gardner, et al., (1984) also noted significantly higher rates of lower respiratory disease among day care infants⁴. Fleming, et al., (1987) reported an increased risk for upper respiratory tract infection associated with day care attendance⁷.

Familial characteristics and genetics may also act as confounders. For instance, in a 1982 publication, Lebowitz, et al., report that an observed relationship between children's pulmonary function and parental smoking disappeared when household aggregation of body mass was taken into account⁸. Another Lebowitz, et al., study (1984) also reported that there was "no remaining independent aggregation of pulmonary function measurements" after familial aggregation of body habitus was controlled for⁹. Genetic predisposition may play a role in respiratory illness and pulmonary function¹⁰; although cross-infection is also involved¹¹.

"Lifestyle" may also act as a confounder. A study in Copenhagen (Holma and Winding, 1977) examined 109 social, medical, housing, and hygiene factors on morbidity. The best predictors for health were "thriving" (satisfaction), followed by "housing standard" and "personal hygiene." The authors reported no effect

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of parental cigarette smoking on the respiratory health of young children¹². A survey of 314 nonsmoking Hong Kong Chinese women and their children and 243 Japanese women and their children reported that chronic cough and sputum symptoms were at least 10 times more prevalent in Hong Kong⁵. This observation was attributed to occupational exposure to dust or fumes and household crowding among the Hong Kong mothers.

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REFERENCES

1. Kerigan, A., et al., "A Three-Year Cohort Study of the Role of Environmental Factors in the Respiratory Health of Children in Hamilton, Ontario," American Review of Respiratory Diseases, 133: 987-993, 1986.
2. Mitchell, E., et al., "Socioeconomic Status in Childhood Asthma," International Journal of Epidemiology, 18(4): 888-890, 1989.
3. Watkins, C.J., et al., "Patterns of Respiratory Illness in the First Year of Life," British Medical Journal, 293: 794-796, 1986.
4. Gardner, G., et al., "Effects of Social and Family Factors on Viral Respiratory Infection and Illness in the First Year of Life," Journal of Epidemiology and Community Health 38(1): 42-48, 1984.
5. Koo, L., et al., "A Comparison of the Prevalence of Respiratory Illness Among Nonsmoking Mothers and Their Children in Japan and Hong Kong," Respiratory Illnesses Among Japanese and Chinese Mothers and Their Children: 290-295, 1988.

2025500574

6. Anderson, L., et al., "Day Care Center Attendance and Hospitalization for Lower Respiratory Tract Illness," Pediatrics 82(3): 300-308, 1988.
7. Fleming, D.W., et al., "Childhood Upper Respiratory Tract infections: To What Degree Is Incidence Affected by Day-Care Attendance?" Pediatrics 79(1): 55-60, 1987.
8. Lebowitz, M., et al., "The Effect of Passive Smoking on Pulmonary Function in Children," Environment International, 8: 371-373, 1982.
9. Lebowitz, M., et al., "Family Aggregation of Pulmonary Function Measurements," American Review of Respiratory Diseases, 129: 8-11, 1984.
10. Colley, J.R.T., et al., "Influence of Passive Smoking and Parental Phlegm on Pneumonia and Bronchitis in Early Childhood," The Lancet II: 1031-1034, 1974.
11. Colley, J.R.T., "Respiratory Symptoms in Children and Parental Smoking and Phlegm Production," British Medical Journal 2: 201-204, 1974.

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12. Holma, B. and Winding, O., "Housing, Hygiene, and Health: A Study in Old Residential Areas in Copenhagen," Archives of Environmental Health 32(2): 86-93, 1977.

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PARENTAL SMOKING: CONFOUNDING VARIABLES

Access to medical care
Age of mother
Air pollution
Birth weight
Breast feeding
Cooking practices/type
Day care attendance
Diet
Family history of illness
Family size
Gender of child
Genetic determinants
Heating type
Home dampness
Hospital spread of illness
Household pets
Newborn illnesses
Nurture
Overcrowding
Parental education
Parental infections
Place of residence
Seasonal variation
Skin test reactivity (allergy)
Socioeconomic status

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I. HEALTH CLAIMS

- The claim that exposure to environmental tobacco smoke (ETS) in the workplace causes disease in nonsmokers is not justified on a scientific basis.

Exposure

- Measurements taken in offices, workplaces and public places indicate that the contribution of tobacco smoke to indoor air is minimal.¹ For example, typical nicotine measurements (which are particularly revealing because nicotine is unique to tobacco smoke) range from an exposure equivalent of 1/100 to 1/1000 of one filter cigarette per hour.² In other words, a nonsmoker would have to spend from 100 to 1000 hours in an office, restaurant or public place in order to be exposed to the nicotine equivalent of just one cigarette.

Lung Function

- A 1980 report³ which concluded that nonsmokers exposed to tobacco smoke at work for 20 or more years had reduced function of the small airways compared to nonsmokers not so exposed still receives considerable attention, although it was heavily criticized for questionable data acquisition and analysis.⁴ In contrast, a more recent study of 1,351 German office workers reportedly found "no evidence" that everyday exposure to

tobacco smoke in the office or at home leads to an essential reduction of lung function in healthy adults.⁵

Lung Cancer

- Nine of the published studies on spousal smoking and lung cancer examined workplace exposure to ETS and the incidence of lung cancer in nonsmokers.⁶ Not one of the studies provides adequate support for an association between ETS exposure in the workplace and lung cancer.

Allergy

- One of the most widespread beliefs, especially in the workplace setting, is that some nonsmokers are "allergic" to tobacco smoke. Scientific researchers, however, have not identified specific allergens in tobacco smoke.⁷ Thus, while some individuals may react to the sight or smell of tobacco smoke, this does not mean that they are experiencing an "allergic" reaction to it.

4. Adlkofer, F., et al., "Small-Airways Dysfunction in Passive Smokers," New Eng. J. of Med. 303(7): 392, 1980.

Huber, G., "Small-Airways Dysfunction in Passive Smokers," New Eng. J. of Med. 303(7): 392, 1980.

Freedman, A., "Small-Airways Dysfunction in Passive Smokers," New Eng. J. of Med. 303(7): 393, 1980.

Aviado, D., "Small-Airways Dysfunction in Passive Smokers," New Eng. J. of Med. 303(7): 393, 1980.

Fountain, L.H., "White-Froeb Study Discredited by Scientists," U.S. Cong. Record, Ninety-Seventh Congress, Second Session, Washington, D.C., U.S. Government Printing Office, E5252-5254, December 16, 1982.

Lebowitz, M., "Influence of Passive Smoking on Pulmonary Function: A Survey," Preventive Medicine 13(6): 645-655, 1984.

5. Kentner, M., et al., "The Influence of Passive Smoking on Pulmonary Function - A Study of 1,351 Office Workers," Preventive Medicine 13(6): 656-669, 1984.

Kentner, M. and D. Weltle, "Passive Tobacco Smoke Inhalation and Lung Function in Adults," Indoor and Ambient Air Quality, eds. R. Perry and P. Kirk, London, Selper Ltd.: 232-241, 1988.

6. Kabat, G. and E. Wynder, "Lung Cancer in Nonsmokers," Cancer 53(5): 1214-1221, 1984.

Garfinkel, L., et al., "Involuntary Smoking and Lung Cancer: A Case-Control Study," JNCI 75(3): 463-469, 1985.

Shimizu, H., et al., "A Case-Control Study of Lung Cancer in Nonsmoking Women," Tohoku J. Exp. Med. 154: 389-97, 1988.

Koo, L., et al., "Measurements of Passive Smoking and Estimates of Lung Cancer Risk Among Non-Smoking Chinese Females," Int. J. Cancer 39: 162-169, 1987.

Wu, A., et al., "Smoking and Other Risk Factors for Lung Cancer in Women," JNCI 74(4): 747-751, 1985.

Lee, P., et al., "Relationship of Passive Smoking to Risk of Lung Cancer and Other Smoking-Associated Diseases," Brit. J. Cancer 54: 97-105, 1986.

Svensson, C. et al., "Smoking and Passive Smoking in Relation to Lung Cancer in Women" Acta Oncologica 28: 623-629, 1989.

Wu-Williams, A., et al., "Lung Cancer Among Women in North-East China," Brit. J. of Cancer 62: 982-987, 1990.

Janerich, D. et al., "Lung Cancer and Exposure to Tobacco Smoke in the Household," New Eng. J. Med. 323(10): 632-636, 1990.

7. Lehrer, S., et al., "Tobacco Smoke Sensitivity: A Result of Allergy?," Ann Allergy 56: 1-10, 1986.

II. SICK BUILDING SYNDROME

- Because it is visible and easily identified by its aroma, environmental tobacco smoke is often blamed for indoor air quality problems. Government and private studies of "sick buildings" in the United States, Canada and Europe report, however, that tobacco smoke may be involved in only two percent to five percent of the buildings investigated for complaints about air quality.¹ For example, from 1981 through 1987, one company studied indoor air quality in 223 different buildings, accounting for over 39 million square feet of property, and found that ETS was a significant concern in only 10, or 4%, of the buildings [Robertson, 1988]. In another SBS database, smoking was implicated as a major contributor to complaints in only 12 of 408 (<3%) of the buildings surveyed [Collett, 1989]. The National Institute for Occupational Safety and Health (NIOSH) investigated more than 200 "sick" buildings and found that tobacco smoke was the source of claimed discomfort in only 2% of the buildings investigated. Ventilation problems were associated with half the complaints; outdoor air was considered a bigger problem than ETS [Melius, 1984]. Other investigators concluded that bacterial and fungal contamination is a major source of indoor air problems [Collett, 1989; Robertson, 1988].

- Inadequate ventilation exacerbates all indoor air quality problems. This suggests that even a total smoking ban is not likely to affect comfort problems in 95 to 98 percent of "sick buildings."²
- The majority of indoor air quality problems in "sick buildings" have been traced to inadequate fresh air and poor air filtration. Because the visibility of tobacco smoke may be an indicator of inadequate ventilation, the prohibition of smoking serves to mask the real reason for poor indoor air quality--lack of proper ventilation. In addition, concentrating on tobacco smoke ignores the fact that adequate ventilation should always be provided in any enclosed space, regardless of whether or not smoking is permitted.

REFERENCES

1. Kirkbride, J., "Sick Building Syndrome: Causes and Effects," Health and Welfare Canada, Ottawa, Canada, 1985.

Melius, J., et al., "Indoor Air Quality -- the NIOSH Experience," Ann. Am. Conf. Gov. Ind. Hydg. 10: 3-7, 1984.

Robertson, G., "Source, Nature and Symptomology on Indoor Air Pollutants," Indoor and Ambient Air Quality, eds. R. Perry and P. Kirk, London, Selper Ltd.: 311-319, 1988.

Collett, C. et al., "A Database of Problem Buildings: Learning by Past Mistakes," Present and Future of Indoor Air Quality, eds. C. Bieva et al.. Amsterdam, Elsevier Science Publishers: 413-419, 1989.

Turner, S. and P. Binnie, "An Indoor Air Quality Survey of Twenty-Six Swiss Office Buildings," Indoor Air '90, Toronto, Canada: 27-32, 1990.
2. Sterling, T. and Kleven, S., "The Epidemiology of 'Sick Public Buildings'," Indoor Air Quality: Symposium, Buenos Aires, National Academy of Sciences of Buenos Aires: 79-107, 1989.

III. VENTILATION

- In 1981, The American Society of Heating, Refrigeration and Air-Conditioning Engineers (ASHRAE) issued a ventilation standard for public places (ASHRAE 62-1981).¹ The Standard established two levels of ventilation, one for areas in which smoking was permitted, and another substantially lower rate for areas where smoking was prohibited. The Standard was recently revised and reissued (ASHRAE 62-1989) with one prescribed ventilation rate, regardless of whether smoking was permitted or not. The decision to reject separate ventilation rates for smoking and nonsmoking areas was influenced by two areas of research: (1) The amount of ventilation required to remove indoor contaminants produced by humans, namely carbon dioxide and body odor, is also sufficient to remove typical amounts of ETS; and (2) ventilation rates for nonsmoking areas under ASHRAE 62-1981 were found to be inadequate and permitted airborne substances to increase, even in the absence of ETS.²
- Operating costs for increasing ventilation to meet specifications set forth in ASHRAE 62-1989 have been estimated at 3-5% over current annual energy expenditures for office buildings. Compliance with ASHRAE Standard 62-1989 will apparently have little effect on annual energy budgets.³

REFERENCES

1. American Society of Heating, Refrigeration and Air Conditioning Engineers, ASHRAE Standard 62-1989, "Ventilation for Acceptable Indoor Air Quality," Atlanta, ASHRAE Publications, 1989.
2. Burroughs, H., "ASHRAE: Addressing the Indoor Air Quality Challenge With Energy Conscious Design," eds. R. Perry and P. Kirk, Indoor and Ambient Air Quality, London, Selper Ltd.: 530-535, 1988.
3. Eto, J., "The HVAC Costs of Increased Fresh Air Ventilation Rates in Office Buildings Part 2," Indoor Air '90, Toronto, Indoor Air '90: 53-58, 1990.

IV. ACCOMMODATION

- Since the claim that exposure to tobacco smoke causes disease in nonsmokers is not scientifically justified,¹ the real issue regarding the "right" to smoke-free air is whether or not smoking should be prohibited because some people consider it to be an annoyance or nuisance.

Annoyance:

- Tobacco smoke may be an annoyance or nuisance to some people, but such complaints typically arise in poorly ventilated areas. Such complaints are most frequently associated with inadequate ventilation and to indoor substances other than ETS [See Section II: "Sick-Buildings"].
- Regulating a behavior such as smoking merely because some see it as an annoyance has undesirable consequences. Numerous individual behaviors could fall into the category of "annoyances," and to demand restrictions on all those potentially "annoying" behaviors is "to call for government regulation of everything."²
- Such regulations also reject the real possibility that people can work things out among themselves and may place a minority

of individuals in the position to dictate what is "right" for everyone.

- The alternative to intrusive regulation is good manners, common courtesy and cooperation between smokers and nonsmokers. This alternative preserves the delicate balance of individual rights and allows for accommodation of everyone's desires.

REFERENCES

1. Wu, J., "Summary and Concluding Remarks," Environmental Tobacco Smoke: Proceedings of the International Symposium at McGill University 1989, eds. D. Ecobichon and J. Wu, Lexington, Massachusetts, Lexington Books: 367-375, 1990.

Layard, M., "Environmental Tobacco Smoke and Cancer: The Epidemiologic Evidence," Environmental Tobacco Smoke: Proceedings 1989: 99-115, 1990.

Wexler, L., "Environmental Tobacco Smoke and Cardiovascular Disease: A Critique of the Epidemiological Literature and Recommendations for Future Research," Environmental Tobacco Smoke: Proceedings 1989: 139-152, 1990.

Witorsch, P., "Effects of ETS Exposure on Pulmonary Function and Respiratory Health in Adults," Environmental Tobacco Smoke: Proceedings 1989: 169-185, 1990.

Adlkofer, F., "Biological Effects After Exposure to ETS," Indoor Air Quality: Symposium, Buenos Aires, National Academy of Sciences of Buenos Aires: 61-76, 1989.

Gostomzyk, G., "Passive Smoking - Report on an International Symposium (23-25 October 1986)," Public Health 49: 212-215, 1987.

Wynder, E. and G. Kabat, "Health Care and Society: Environmental Tobacco Smoke and Lung Cancer," Present and Future of Indoor Air Quality, eds. C. Bieva et al., Amsterdam, Elsevier Science Publishers: 135-145, 1989.
2. Williams, W., "Cigarettes and Property Rights," Clearing the Air: Perspectives on Environmental Tobacco Smoke, ed. R. Tollison, Lexington, Massachusetts, D.C. Heath and Company: 39-52, 1988.

The Separation Issue:

- The 1986 Report of the Surgeon General on ETS suggests that separation of smokers and nonsmokers is not effective in minimizing the nonsmoker's exposure to ETS. That claim was made without scientific support. Indeed, subsequent research indicates that simple separation of smokers and nonsmokers effectively minimizes ETS exposures for nonsmokers.¹⁻³
- One recent study reported that the use of designated smoking areas reduced exposure to ETS by 95%.¹ Another study of a smoking-restricted office building reported that ambient nicotine in nonsmoking areas was virtually undetectable, suggesting that ETS had a negligible impact on the nonsmoking areas of the building.²
- Canadian researchers, in a series of reports, presented results on levels of ETS constituents in offices where smoking was regulated and unregulated. They reported no significant differences in average ETS constituent levels between nonsmoking offices that received recirculated air from designated smoking areas and nonsmoking offices that did not receive recirculated air.³ They concluded:

The results indicate that the provision of a designated, but not separately ventilated smoking area can effectively eliminate or

drastically reduce most components of environmental tobacco smoke from nonsmoking offices.

- A federally-sponsored study of ETS in aircraft cabins indicates that separation of smokers and nonsmokers is an effective measure for reducing exposure to ETS.⁴ The authors reported that ETS constituent concentrations in nonsmoking sections were below the limit of detection. Similar results have been reported in other studies.⁵